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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

Multiple organ failure: from basic science to prevention

Multiple organ failure is a modern epidemic, first described in the mid-1970s [1, 2]. This syndrome of multiple organ failure is both the *raison d'etre* and the consequence of skilled intensive care medicine, created by our success in providing sophisticated organ system support to patients who, a few years ago, would have died rapidly from their acute disease. Although many of these patients now survive, the cost of success is high. The mortality from multiple organ failure increases with the number and duration of failing organs [3], and as it costs twice as much to die in an intensive care unit as it does to survive [4], the resources required to generate a survivor are considerable. For those patients destined to die, prognostic uncertainty encourages protracted organ system support [5], with the result that death is merely deferred at greater expense. The challenge for intensive care medicine is to develop cost-effective methods for improving survival rates, while reducing expenditure on those who ultimately will die. Efforts to identify patients who cannot benefit from continued support have not been successful, primarily because group probabilities cannot be used to predict outcome for individual patients. Similarly, the biotechnological approach to sepsis has consumed a considerable amount of venture capital with, as yet, little evident return on the investment. A different approach is needed which links the pathogenesis of multiple organ failure with its prevention, and with techniques to restore cellular and organ function.

This postgraduate issue of the journal is a joint venture between the Intensive Care Society and the *British Journal of Anaesthesia*. The reviews consider the mechanisms by which organ failures occur and methods for limiting cellular damage and restoring lost function. While the factors which precipitate cell injury and organ failure are amenable to relatively simple preventative interventions, once damage has occurred the process becomes increasingly complex and self-sustaining. Natural defence systems may become pathologically hyperactive, or suppressed at different stages of critical illness, making it difficult to target therapies directed at the immuno-inflammatory cascade with any degree of accuracy or safety. The prevention of critical illness must become a priority, but to do so successfully depends on developing better systems for identifying patients at risk [6], as well as understanding the pathophysiology of multiple organ failure. Considerable research investment is needed to assess the factors which determine susceptibility to, and recovery from, this syndrome.

In this postgraduate issue the reader will find views on the present state of knowledge with regard to cells, the gastrointestinal tract, nutrition, infection, the lung, kidney and liver and their place in multiple organ failure. Current therapy is outlined and there are clear indicators for future research. The busy clinician may be forgiven for wondering why there is little mention of the day-to-day problems which beset every intensive care unit; the "real world–coal face" issues of apparent lack of resources, staffing, equipment, etc. These are important matters, but result from the unrelenting and, to a great extent, unregulated demand for intensive care. This demand cannot be met by spending more money alone, as was demonstrated in the USA in a recent budget year where 1% of its gross domestic product was spent on intensive care medicine. The return on this enormous investment was difficult to assess and although improvement in outcome was demonstrated in some areas, continued spending at the 1% level could not be justified. In the United Kingdom there is a shortage of intensive care beds brought recently to public attention by a number of patients ferried around the country seeking a bed under the full glare of the media spotlight. These events led to a Government commitment to consider more resources for intensive care. Nevertheless, it is unlikely that these will be sufficient to satisfy the current demand; indeed the American experience suggests that even unlimited resources would not be cost-effective unless carefully targeted. This issue of the journal should, at the very least, be helpful for the clinician in deciding where scarce resources should best be spent as they become available.

As intensive care medicine progresses towards independent specialty status, this is perhaps an opportune moment to acknowledge the substantial contribution which anaesthesia has made both to the service and science of intensive care medicine. We hope that the good relationships which exist between intensive care medicine and all the other major disciplines will foster further collaborative activities of this type, with a particular emphasis on drawing together clinical research with the basic sciences.

JULIAN BION
Intensive Care Society
L. STRUNIN
Postgraduate Editor
British Journal of Anaesthesia

References

1. Baue AE. Multiple, progressive, or sequential systems failure: a syndrome of the 1970s. *Archives of Surgery* 1975; **110**: 779–781.
2. Eisman B, Beart R, Norton L. Multiple organ failure *Surgery Gynecology and Obstetrics* 1977 **144**: 323–326
3. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. *Annals of Surgery* 1985; **202**: 685–693.
4. Sage WM, Rosenthal MH, Silverman JF. Is intensive care worth it? An assessment of input and outcome for the critically ill. *Critical Care Medicine* 1986; **14**: 777–782.
5. Detsky AS, Stricker SC, Mulley AG, Thibault GE. Prognosis, survival, and the expenditure of hospital resources for patients in an intensive care unit. *New England Journal of Medicine* 1981; **305**: 667–672.
6. Bion J. Rationing intensive care. *British Medical Journal* 1995; **310**: 682–683.

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Mechanisms of cell injury and death

J. P. Cobb, R. S. Hotchkiss, I. E. Karl and T. G. Buchman

Control of the rate of cell death relative to the rate of cell division maintains organ integrity and physiological homeostasis. Cell death is valuable for the organism because it removes terminally injured or unwanted cells that utilize valuable substrates and nutrients. Likewise, cell death also has value for the species, as it provides a mechanism for eliminating terminally injured individuals who consume necessary societal resources or harbour toxic pathogens. Recent advances in cellular biology have contributed substantially to our understanding of the processes of cell injury and death, and have provided the molecular tools necessary to control it. This paper reviews cell injury and adaptation; mechanisms of cell death; the roles of cell injury and death in the pathophysiology of organ dysfunction; and implications for prevention and therapy of multiple organ dysfunction syndrome (MODS).

Cell injury and adaptation

Cell injury occurs as a result of physical, chemical or biological insults or as a result of vital substrate deficiency (table 1). The cellular response to these injuries is adaptive, designed to restore homeostasis and protect the cell from further injury. Although characteristic changes in gene transcription occur, it is not the relative amount but the pattern of transcription that changes, with emphasis directed towards transcription of "vital" genes. The responses induced by cellular injury fall into four main patterns: the ischaemic/anoxic, oxidative, heat shock and acute phase responses. These are reviewed briefly below.

ISCHAEMIC/ANOXIC STRESS RESPONSE [13]

Because of the unusual high efficiency of the cardiopulmonary system to transport oxygen, cells in higher animals have not developed elaborate cellular pathways to adapt to hypoxia and are thus relatively sensitive to ischaemia [13, 18]. As a consequence, lack of oxygen dramatically increases the need for anaerobic glycolysis to maintain intracellular ATP reserves. The associated changes in gene expression include decreased total protein synthesis, induction of hypoxia-associated proteins (e.g. glyceraldehyde-3-phosphate dehydrogenase, a glycolytic enzyme), induction of the heat shock response (see below), and induction of glucose-regulated proteins. If these changes are inadequate to prevent ATP depletion, membrane ion pumps fail and membrane integrity is lost. Increased intracellular Ca^{2+} occurs and a variety of degradative processes are initiated, leading to cytoplasmic swelling and eventual cell death.

OXIDATIVE STRESS RESPONSE [9]

Agents that provoke oxidative injury include products of oxidative metabolism (especially from the mitochondria) and those released from activated phagocytes. Collectively, they are called *reactive oxygen species* (ROS), and include superoxide, hydrogen peroxide, hydroxyl radical (the generation of which depends on availability of ferrous ion and superoxide) and nitric oxide. Iron, which is essential for DNA synthesis and oxidative metabolism, also catalyses the Fenton and Haber-Weiss reactions, converting superoxide to molecular oxygen and hydrogen peroxide to the hydroxyl radical. Under normal conditions, free iron is compartmentalized by the protein ferritin, which "protects" the cell by keeping iron in a non-reactive crystallized core as ferric ion (Fe^{3+}). The results of the oxidative reactions of ROS include de-energization of mitochondria and loss of energy stores, peroxidation and disruption of lipid membranes, and direct DNA damage.

The adaptive response of the cell to oxidative stress includes both enzymatic and non-enzymatic capacities and induction of oxidative stress response proteins [9]. Superoxide dismutase reduces superoxide to molecular oxygen and hydrogen peroxide; catalase catalyses the conversion of this hydrogen peroxide to oxygen and water. Reduced glutathione (which reacts with hydrogen peroxide in the presence of glutathione peroxidase to form water and oxidized glutathione), vitamin C and vitamin E constitute the

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Key words

Cells, apoptosis. Cells, necrosis. Cells, death. Complications, sepsis.

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Table 1 Mechanisms of cell injury

- (1) Physical
  - (a) ionizing radiation
  - (b) temperature
  - (c) mechanical trauma
- (2) Chemical
  - (a) drugs
  - (b) poisons
- (3) Biological
  - (a) enzymes
  - (b) cytokines
  - (c) viral infection
  - (d) cell-mediated
- (4) Critical substrate deficiency
  - (a) oxygen
  - (b) glucose

major intracellular reducing (non-enzymatic) agents. Several proteins are induced under oxidative stress, the most important of which may be metallothionein, which binds not only heavy metals but also ROS via the free sulphydryl groups of its many cysteine residues. ROS also activate the transcriptional factors AP-1 and NFκB, both of which promote transcription of cytokines and have been associated with induction of apoptotic cell death (see below). If these adaptive responses are inadequate to prevent depletion of cellular glutathione, then cell protein thiol groups become the remaining reducing agents, leading to loss of critical enzymatic function and cell death.

HEAT SHOCK RESPONSE [10, 20]

The highly conserved cellular response to heat, known as the heat shock response, is associated with induction of *heat shock proteins* (HSP). The most extensively studied are the HSP 70 family, which includes stress-induced HSP 72. Interestingly, HSP also are induced by a variety of other cellular insults, including ischaemia/reperfusion, oxidative stress, exposure to heavy metals (e.g. arsenite) and infection. For this reason, the heat shock response is called simply the "stress response", and HSP are known as "stress proteins". Control of HSP transcription is mediated by heat shock element activation in the heat shock protein promoter region. HSP aid in the proper folding of newly translated proteins, and are referred to as "molecular chaperones". Increased production of HSP is believed to provide an adaptive advantage to stressed cells by increasing the fidelity of protein synthesis and aiding refolding of damaged or denatured proteins.

ACUTE PHASE RESPONSE [26]

Although "acute phase response" can refer to the response of any tissue to injury, its use is commonly restricted to the dramatic change in the pattern of hepatocyte protein synthesis. The most important stimuli are interleukin 1 (IL-1), tumour necrosis factor (TNF), and IL-6, products of macrophage/monocyte activation. The hepatocyte response to these cytokines is an outpouring of plasma proteins that function to maintain the homeostasis of the organism. They include C-reactive protein, fibrinogen, complement, the metal binding proteins haptoglobin and ferritin, and plasminogen activator inhibitor and many others. The acute phase response (activation) of endothelial cells includes increased surface expression of adhesion, selectin and integrin molecules that facilitate leucocyte adhesion and release of IL-1, IL-6, IL-8 and platelet activating factor (PAF).

Mechanisms of cell death

If the genetic and metabolic adaptive responses described above are inadequate for a given injury, the cell will die. Increased interest in the mechanisms responsible for cell death, however, has made it clear that morphological classification of cell death requires revision. At least two types of cell death have been described. In the first, cell damage is manifested by cytoplasmic swelling, plasma membrane blebbing, dilation of the endoplasmic reticulum and mitochondria, dissolution of chromatin and, finally, interruption of membrane integrity. The other, less frequently observed type of cell death was described by Kerr [16] and called *shrinkage necrosis*. It is manifested by cytoplasmic shrinkage, larger plasma membrane buds and nuclear chromatin condensation. Both types of cell death result in the generation of necrotic debris that is engulfed by phagocytic cells.

TERMINOLOGY

The morphological changes described above are not restrictive. Nuclear condensation and mitochondrial swelling, for example, have been observed in both swelling and shrinkage types of cell death. There is also clear evidence of significant overlap between them at the molecular level (see below) [11, 14, 18]. Moreover, there is considerable imprecision in the literature regarding the terminology of cell death. Historically, *necrosis* has been the term used to refer to cell death in general. The term *apoptosis* (coined by Kerr, Wyllie, and Currie from the Greek word meaning "dropping off", as in leaves dropping from a tree [17]) is now used specifically to describe death manifested by cell shrinkage. Apoptosis is responsible for the ordered, normal cell death of intestinal epithelial cells and blood neutrophils.

Programmed cell death, which refers to the ordered death of cells during embryogenesis, however, is also characterized by cell shrinkage. Apoptosis and programmed cell death are frequently, but incorrectly, used interchangeably. The question of what to call non-apoptotic cell death has been problematic. *Necrosis*, a leading contender, is also used to refer to the process of removal of the cellular remains of apoptosis (so-called "post-apoptotic necrosis" [18]) [11, 32]. This degree of imprecision led Farber recently to remark that "there is no field of basic cell biology and cell pathology that is more confusing and unintelligible than is the area of *apoptosis versus necrosis*" [11]. Consequently, several

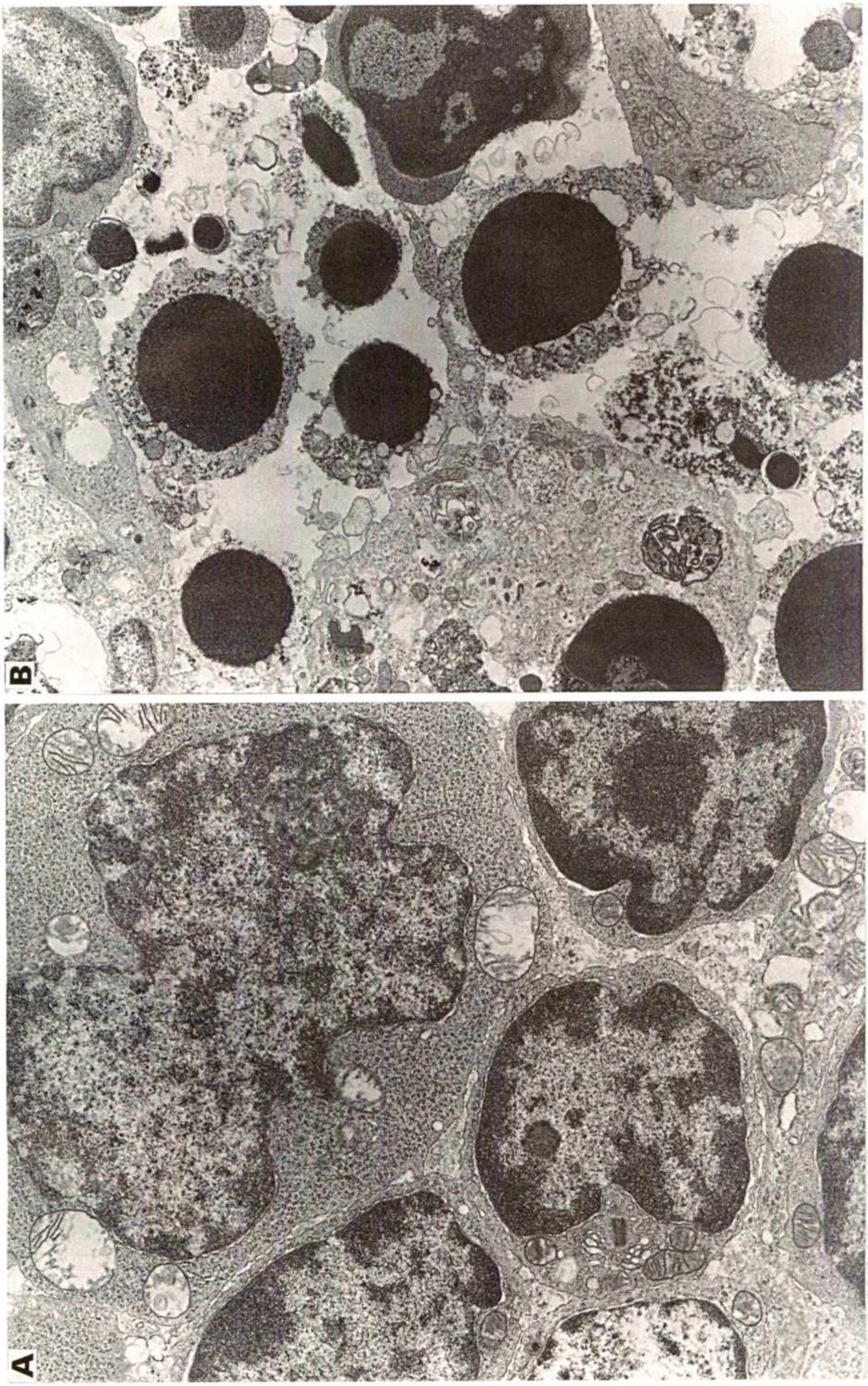

Figure 1 Electron micrographs of murine thymocytes from normal (A, sham laparotomy) and septic (B, caecal ligation and puncture) mice. Note the differences in the pattern and distribution of chromatin. Compared with controls (A), thymocytes from septic animals (B) demonstrate nuclear condensation and cell shrinkage, consistent with apoptosis.

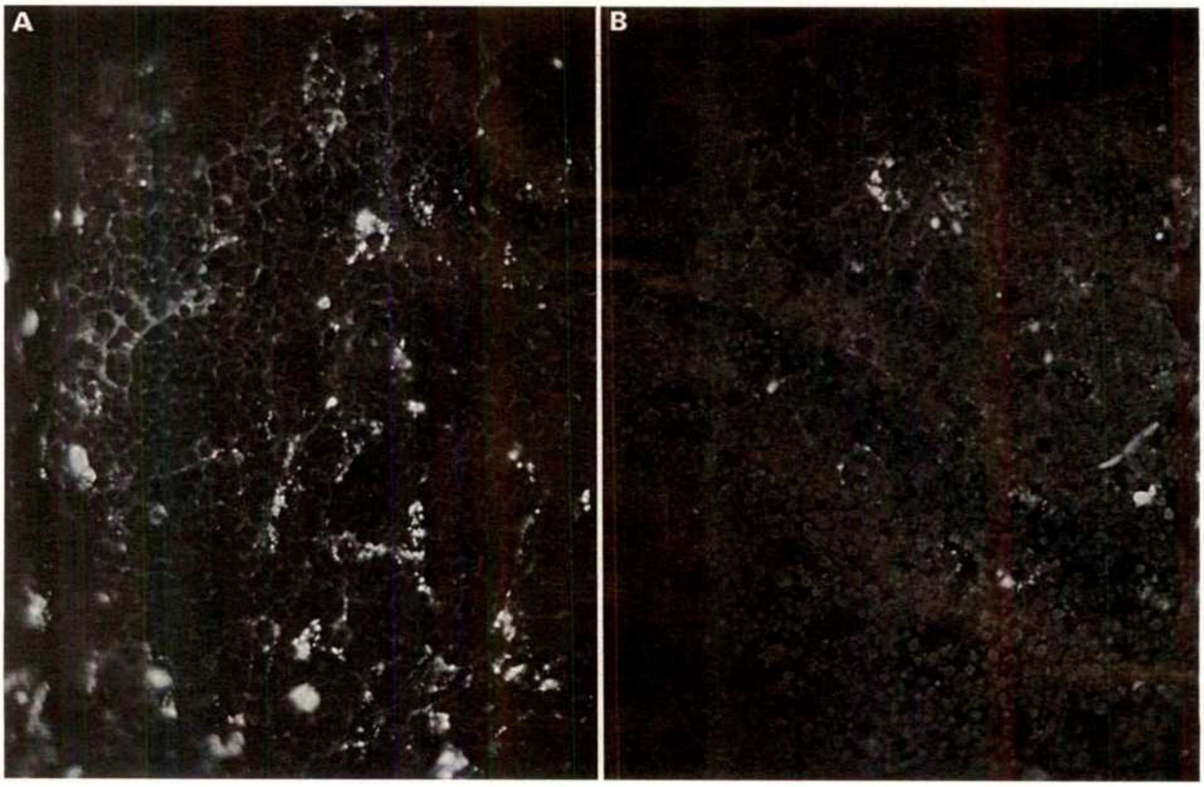

Figure 2 Micrographs (×360 magnification) of murine thymocytes from normal (A, sham laparotomy) and septic (B, caecal ligation and puncture) mice photographed using the fluorescent TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end-labelling) technique. Cells are permeabilized and treated with fluorescein labelled dUTP and terminal deoxynucleotide transferase. Note that in the control mice, all nuclei appear dark (A). In contrast, nuclei of septic mice (B) are fluorescent, consistent with DNA strand breaks and apoptosis.

authors have reviewed this subject in an attempt to standardize terminology and separate the process from the morphology of cell death [11, 14, 15, 18].

PROCESS OF CELL DEATH

From a pathological standpoint, it is important to distinguish between the process of cells dying *per se* from the changes that occur in cells after death [11, 18]. Majno and Joris [18] have characterized the *process* of cell death as (1) cell death by ischaemia, (2) cell death by accident, or (3) cell death by suicide. Accidental cell death is used to describe death as a result of an external agent or toxin. Both cell death secondary to ischaemia and accident are usually characterized morphologically by cell swelling. In this type of cell death, interference with ATP generation secondary to hypoxia or toxin-induced increases in plasma membrane permeability produce membrane failure. Reversible consequences of injury include cytoplasmic blebbing, nuclear chromatin condensation, dilation of the endoplasmic reticulum, condensation then swelling of mitochondria and activation of stress response genetic programmes (described above). Continued injury results in interruptions of membrane integrity, dissolution of chromatin, and calcifications within mitochondria, all of which are signs of irreversible cell injury and death. Majno and Joris [18] have suggested the term *oncosis*, from the Greek word meaning "swelling", for this type of cell death. *Necrosis* is the morphological term used for the cellular debris remaining after either oncosis or apoptosis [18].

Death by suicide refers to the process of cell death in which injury activates a highly conserved programme of "suicide" genes that engineer death of the cell. This process typically results morphologically in apoptosis. Interest in cell death by suicide (apoptosis) has gained considerable momentum recently as the disorders associated with apoptotic cell death have expanded to include cancer, autoimmunity, inflammation, infection, AIDS, neurodegeneration and myelodysplasia [31]. The molecular trigger responsible for induction of apoptosis is incompletely defined, but appears to be present in all mammalian cells at all times and is conserved across species. Not surprisingly, induction of apoptosis is tightly controlled. Several regulatory genes have been identified, including the Bcl-2 family, p53 and Fas [21, 25]. The molecular machinery responsible (the "executioner") includes a cysteine protease (CPP-32 in mammals) that may inactivate DNA repair enzymes [19, 23, 35]. The cellular changes characteristic of apoptosis include a "flip" of phosphatidylserine from the inside to the outside surface of the cell membrane [33], cytoplasmic shrinkage, little or no swelling of organelles (mitochondria), membrane budding and fragmentation that include mitochondria or nuclear fragments, and chromatin condensation consisting of DNA fragments. These membrane changes lead to rapid recognition and cell elimination by neighbouring phagocytes, which may make apoptotic cells difficult to locate using conventional microscopic techniques. The techniques that are used to detect apoptosis include light and electron microscopy (fig.

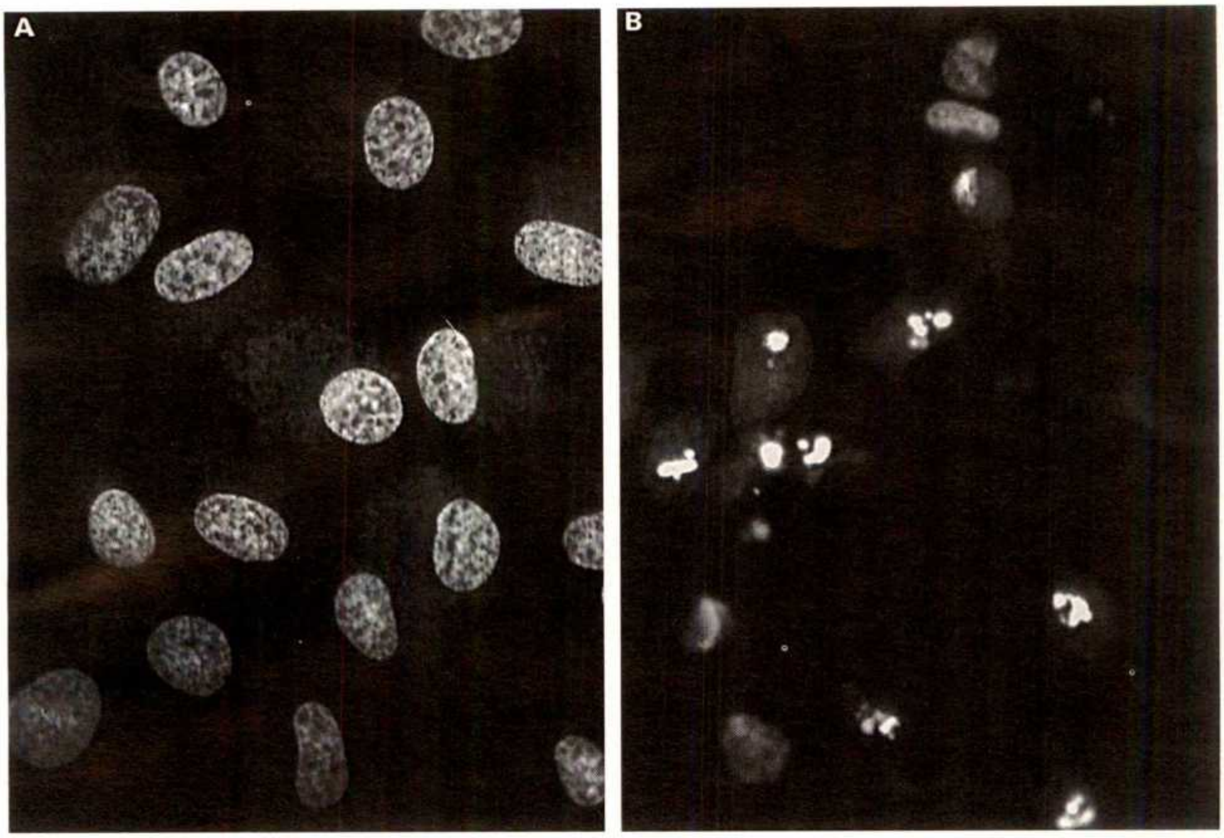

Figure 3 Normal cultured porcine aortic endothelial cells (A, × 360 magnification) stained with nuclear binding dye Hoechst 33342. The nuclei are smooth and ovoid. Nuclei from cells challenged with endotoxin followed by arsenite are compact and fragmented ("apoptotic bodies", B, × 360 magnification).

Table 2 Comparison of characteristics of oncosis and apoptosis

Oncosis—death by swelling	Apoptosis—death by shrinkage
(1) Swelling of organelles and cytoplasm	(1) Shrinkage of cytoplasm
(2) Small dense chromatin clumps which are not sharply defined	(2) Large, dense, often crescent-shaped aggregates of chromatin and nuclear fragmentation
(3) Swelling and eventual disintegration of organelles (e.g. mitochondria and endoplasmic reticulum)	(3) Organelles maintain structural integrity
(4) Early focal disruption of the plasma membrane with blebbing	(4) Plasma membrane maintains integrity early; later stage characterized by budding of membrane, frequently containing organelles
(5) DNA agarose gel electrophoresis demonstrates smear pattern indicative of randomized breakdown	(5) DNA agarose gel electrophoresis demonstrates "ladder" pattern of discrete internucleosomal breakdown
(6) Cells rupture and contents are released causing inflammatory response	(6) Cells are either ingested whole by phagocytic cells, or they break into membrane-bound fragments (apoptotic bodies) which then are ingested

1), end-labelling of DNA fragments (fig. 2), DNA agarose gel electrophoresis and binding of nuclear-specific dyes (fig. 3).

Despite the relatively clear distinction which can be made morphologically (oncosis *versus* apoptosis is compared in table 2), examination at the molecular level demonstrates considerable overlap. For example, both oncosis and apoptosis have been associated with increases in intracellular Ca^{2+}, which activate a number of enzymes including phospholipases, endonucleases, proteases and protein kinases. In addition, the adaptive response to ischaemic, inflammatory, oxidant and heat-induced stress involve changes in gene expression that are shared by both types of cell death. Further, the same type of injury can result in cell death by either mode. Indeed, Kerr's original description of apoptosis ("shrinkage necrosis") was based upon differentiation of shrunken necrotic cells from the more common swollen necrotic cells in ischaemic liver tissue [16].

Pathophysiology of organ dysfunction

Studies of cellular responses *in vivo* indicate that injury activates the programmes of stress gene expression reviewed above. For example, the hepatocellular response to ischaemic injury in a porcine model of MODS includes activation of the acute phase, oxidative, and heat shock responses [7]. In contrast, neighbouring hepatic endothelial cells in this model did *not* stain for heat shock gene expression (*in situ* hybridization), suggesting that there are cell-specific differences in the genetic response to similar injury. A subsequent investigation conducted *in vitro* under more controlled conditions explored the time-course and interaction of these cellular stress responses. Human hepatoblastoma (HepG2) cell lines were treated with inducers of the acute phase response (IL-1 and TNF) and heat shock responses separately and in combination. The results indicated that shock-induced expression of these responses were distinct, exclusive and prioritized [6]. Specifically, the heat shock stress response, the most primitive and highly conserved of stress gene responses, was capable of extinguishing expression of other genetic programmes [5, 28]. These data suggest that hepatocyte injury of sufficient severity to trigger the heat shock response can prevent production of system-stabilizing acute phase proteins and other adaptive responses. The liver's response to such a systemic injury, from the host's perspective, would appear to be inadequate and indicative of failure. Hepatic dysfunction in this model of MODS, thus, would result from execution of primitive, protective genetic responses that give individual cells priority over the organism.

The sequence of stress gene programme activation also appears to be important. In one *in vitro* model, the endothelial cell response to arsenite, an inducer of the heat shock response, and to endotoxin, an inducer of the acute phase response, were studied. The results indicated that induction of the heat shock response could protect against endotoxin-induced cytotoxicity, but reversing the order—endotoxin challenge followed by induction of the heat shock response—increased cell death by apoptosis [5]. The effect of the heat shock response was not the result of a detrimental effect of the heat shock proteins themselves, but rather to the heat shock-induced inhibition of further protein synthesis [5]. An important hypothesis drawn from these data is that two independent programmes of stress gene expression can interact, depending on the sequence, to either protect the cell or trigger cell death by suicide (apoptosis). This may explain the absence of endothelial cells expressing heat shock proteins after shock *in vivo* ([7], discussed above), as endothelial cell apoptosis may have resulted in their subsequent removal by phagocytes before *in situ* staining. Thus, endothelial cell dysfunction and death in this model result from the adverse interaction of two usually beneficial patterns of stress responses. The mechanism responsible may involve alterations in the cellular redox potential and changes in nuclear transcription factor activity [unpublished observations]. For example, in the cultured endothelial cell model, reducing agents such as *N*-acetyl-L-cysteine and dithiothreitol block induction of endotoxin/arsenite-induced endothelial cell apoptosis, implicating ROS in the induction of apoptotic cell death [1, 2]. This raises the possibility that the adaptive response produced by oxidative stress could modulate the interaction of the acute phase and heat shock responses, and may participate in determining the fate of the cell.

Apoptosis may also contribute to failure of organs in other settings, in particular, septic shock. Injection of Gram-negative or Gram-positive bacteria [34], endotoxin [34, 36], or caecal ligation and puncture [4] induced apoptosis in rodent thymocytes. Zhang and colleagues [36] reported that mice injected with lipopolysaccharides had apoptosis not only in the thymus, but also in the spleen, bone marrow and endothelial cells. Norimatsu and associates injected swine intravenously with 0.5 mg kg^{-1} *Escherichia coli* endotoxin and noted that cells in both thymus and mesenteric lymph nodes underwent apoptosis [24]. In a recent report, Rogers and colleagues demonstrated apoptosis in the liver of mice infected with *Listeria monocytogenes* [27]. Apoptosis has also been reported in rabbit heart [12] and rat kidney [29] after ischaemia/reperfusion injury. Collectively, these investigations suggest that apoptotic cell death may be a principal mechanism responsible for organ dysfunction and death as a consequence of shock-induced injury.

Conclusions—from basic science to therapy and prevention

Cell injury occurs as a result of physical, chemical or biological insults or from vital substrate deficiency. These insults induce expression of adaptive stress response gene programmes that include the ischaemic/hypoxic stress, oxidative stress, heat shock and acute phase responses. If the severity of the injury exceeds the ability of the cell to adapt, then cell death occurs. The processes of cell death include cell death by ischaemia, accident or suicide. Morphologically, ischaemic and accidental deaths are usually manifested by cytoplasmic swelling (*oncosis*) and suicidal cell death by cytoplasmic shrinkage (*apoptosis*). However, this terminology lacks precision, as some "accidental" causes of cell death, such as heat, can also induce apoptosis [18]. The molecular machinery responsible for cell death and the boundaries between apoptosis and other modes of cell death remain to be determined [14].

The sequence and interaction of the acute phase, heat shock and oxidative stress responses appear to be a determinant of the fate of the cell. The pattern of cell responses is injury- and tissue-dependent and may help to explain differences in the course and nature of organ failure. Specifically, it appears that stimuli sufficient to trigger the heat shock response can precipitate cell (and organ) failure by blocking initiation of other programmes of stress gene expression (e.g. the system stabilizing acute phase response of hepatocytes). In other cells (e.g. the endothelium), the sequence of acute phase followed by heat shock response may result directly in apoptotic cell death. The function of shock-induced apoptosis is not known, but it may contribute to control of immune cell proliferation in thymus, spleen, bone marrow, and lymph nodes and modulation of the inflammatory response.

MODS is the result of cellular responses to a stimulus of either enormous magnitude or distribution. The stimulus itself frequently does not result directly in cell death, but rather the magnitude of the appropriate response from stimulated cells collectively is injurious to the organism. For instance, small doses of i.v. lipopolysaccharide (endotoxin) in humans are not directly cytotoxic, but lead to the release of the intercellular mediators, such as cytokines, that amplify the stimulus and trigger organ dysfunction [30]. Unfortunately, attempts to attenuate the magnitude of this response by attacking the circulating mediators themselves (e.g. anti-endotoxin and anti-cytokine therapies) have failed to improve patient survival in randomized, prospective trials [22]. These negative data forced a broad re-examination of the treatment strategies for the systemic inflammatory response syndrome (SIRS) and MODS and a change in focus from extracellular signals (i.e. the mediators) to the intracellular responses to these signals [8]. Recent symposia have addressed this important issue (e.g. "The Future of Sepsis Research", August 1995, Bethesda, MD, USA, sponsored by the American College of Chest Physicians, National Institute of Allergy and Infectious Disease, National Heart, Lung, and Blood Institute and National Institutes of Health, USA).

A NEW THERAPEUTIC STRATEGY: MODULATION OF CELLULAR RESPONSES TO INJURY

In summary, the data presented above are consistent with a new hypothesis on the cellular origin of MODS, one that has emerged as a result of a change in focus from the extracellular to the intracellular response to injury. They suggest that there are distinct, exclusive, and prioritized genetic programmes expressed in response to cell injury that are specific to cell type and injury. The effects of these stress response gene programmes are usually cytoprotective, but when activated in sequence, they can precipitate apoptotic cell death. Recent success in modulating induction of apoptosis with reducing agents [1], anti-oxidants [2], inhibitors of protein synthesis [5], anti-TNF antibody [34] and steroid antagonists [3] suggests that pharmacological control in the clinical setting is possible. A complete understanding of the type, sequence, interaction and impact of stress gene responses to injury will form the basis for novel gene-directed therapy for the treatment and prevention of MODS.

References

1. Abello PA, Fidler SA, Buchman TG. Thiol reducing agents modulate induced apoptosis in porcine endothelial cells. *Shock* 1994; **2**: 79–83.
2. Abello PA, Fidler SA, Bulkley GB, Buchman TG. Antioxidants modulate induction of programmed endothelial cell death (apoptosis) by endotoxin. *Archives of Surgery* 1994; **129**: 134–140.
3. Ayala A, Herdon CD, Lehman DL, DeMaso CM, Ayala CA, Chaudry IH. The induction of accelerated thymic programmed cell death during polymicrobial sepsis: control by corticosteroids but not tumour necrosis factor. *Shock* 1995; **3**: 259–267.
4. Barke RA, Roy S, Chapin RB, Charboneau R. The role of programmed cell death (apoptosis) in thymic evolution following sepsis. *Archives of Surgery* 1994; **129**: 1256–1262.
5. Buchman TG, Abello PA, Smith EH, Buckley GB. Induction of heat shock response leads to apoptosis in endothelial cells previously exposed to endotoxin. *American Journal of Physiology* 1993; **265**: H165–H170.
6. Buchman TG, Cabin DE. Molecular biology of circulatory shock III. HepG2 cells demonstrate two patterns of shock-induced gene expression which are independent, exclusive, and prioritized. *Surgery* 1990; **108**: 902–911.
7. Buchman TG, Cabin DE, Vickers S, Deutschman CS, Delgado E, Sussman MM, Bulkley GB. Molecular biology of circulatory shock II: Expression of four groups of hepatic genes is enhanced following resuscitation from cardiogenic shock. *Surgery* 1990; **108**: 559–566.
8. Buchman TG, Zehnbauer BA. Molecular biology in the intensive care unit: a framework for interpretation. *New Horizons* 1995; **3**: 139–145.
9. Camhi SL, Lee P, Choi AMK. The oxidative stress response. *New Horizons* 1995; **3**: 170–182.
10. De Maio A. The heat-shock response. *New Horizons* 1995; **3**: 198–207.
11. Farber E. Programmed cell death: necrosis versus apoptosis. *Modern Pathology* 1994; **7**: 605–609.
12. Gottlieb RA, Burleson KO, Kloner RA, Babior BM, Engler RL. Reperfusion injury induces apoptosis in rabbit cardiomyocytes. *Journal of Clinical Investigation* 1994; **94**: 1621–1628.
13. Graven KK, Farber HW. Hypoxia-associated proteins. *New Horizons* 1995; **3**: 208–218.
14. Hockenbery D. Defining apoptosis. *American Journal of Pathology* 1995; **146**: 16–19.
15. Kane AB. Redefining cell death. *American Journal of Pathology* 1995; **146**: 1–2.
16. Kerr JFR. Shrinkage necrosis: a distinct mode of cellular death. *Journal of Pathology* 1971; **105**: 13–20.
17. Kerr JFR, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer* 1972; **26**: 239–257.
18. Manjo G, Joris I. Apoptosis, oncosis and necrosis. *American Journal of Pathology* 1995; **146**: 3–15.
19. Martin SJ, Green DR. Protease activation during apoptosis: death by a thousand cuts? *Cell* 1995; **82**: 349–352.
20. Minowada G, Welch WJ. Clinical implications of the stress response. *Journal of Clinical Investigation* 1995; **95**: 3–12.
21. Nagata S, Golstein P. The Fas death factor. *Science* 1995; **267**: 1449–1456.
22. Natanson C, Hoffman WD, Suffredini AF, Eichacker PQ, Danner RL. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Annals of Internal Medicine* 1994; **120**: 771–783.
23. Nicholson DW, Ali A, Thornberry NA, Vaillancourt JP, Ding CK, Gallant M, Gareau Y, Griffin PR, Labelle M, Lazebnik YA, Munday NA, Raju SM, Smulson ME, Yamen T, Yu VL, Miller DK. Identification and inhibition of the ICE/CED-3 protease necessary for mammalian apoptosis. *Nature* 1995; **376**: 37–43.
24. Norimatsu M, Ono T, Aoki A, Ohishi K, Takahashi T, Watanabe G, Taya K, Sasamoto S, Tamura Y. Lipopolysaccharide-induced apoptosis in swine lymphocytes *in vivo*. *Infection and Immunity* 1995; **63**: 112–116.
25. Olvati ZN, Korsmeyer SJ. Checkpoints of dueling dimers foil death wishes. *Cell* 1995; **79**: 189–192.
26. Pannen BHJ, Robotham JL. The acute phase response. *New Horizons* 1995; **3**: 183–197.
27. Rogers HW, Callery MP, Deck B, Unanue ER. *Listeria monocytogenes* induces apoptosis of infected hepatocytes. *Journal of Immunology* 1996; **156**: 679–684.
28. Schoeniger LO, Reilly P, Bulkley GB, Buchman TG. Molecular biology of circulatory shock V: Heat shock gene expression excludes hepatic acute phase gene expression following resuscitation from hemorrhagic shock. *Surgery* 1992; **112**: 355–363.
29. Schumer M, Colombel MC, Sawczuk IS, Gobe G, Connor J, O'Toole KM, Ollsson CA, Wise GJ, Buttyan R. Morphologic, biochemical, and molecular evidence of apoptosis during the reperfusion phase after brief periods of renal ischemia. *American Journal of Pathology* 1992; **140**: 831–838.

30. Taveira Da Silva AM, Kaulbach HC, Chuidian FS, Lambert DR, Suffredini AF, Danner RL. Brief report: shock and multiple-organ dysfunction after self-administration of Salmonella endotoxin. *New England Journal of Medicine* 1993; **328**: 1457–1460.
31. Thompson CB. Apoptosis in the pathogenesis and treatment of disease. *Science* 1995; **267**: 1456–1462.
32. Trump BF, Berezesky IK. Calcium-mediated cell injury and cell death. *FASEB Journal* 1995; **9**: 219–228.
33. Vermes I, Haanen C, Steffens-Nakken H, Reutelingsperger C. A novel assay for apoptosis. Flow cytometric detection of phosphatidylserine expression on early apoptotic cells using fluorescein labelled Annexin V. *Journal of Immunological Methods* 1995; **184**: 39–51.
34. Wang S-D, Huang KJ, Lin YS, Lei HY. Sepsis-induced apoptosis of the thymocytes in mice. *Journal of Immunology* 1994; **152**: 5014–5023.
35. Whyte M, Evan G. Apoptosis: the last cut is the deepest. *Nature* 1995; **376**: 17–18.
36. Zhang XM, Morikawa A, Takahashi K, Jiang GZ, Kato Y, Suglyama T, Kawal M, Fukada M, Yokochi T. Localization of apoptosis (programmed cell death) in mice by adminstration of lipopolysaccharide. *Microbiology and Immunology* 1994; **38**: 669–671.

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The immuno-inflammatory cascade

H. F. Galley and N. R. Webster

Severe sepsis complicated by multi-organ dysfunction syndrome (MODS) is a major cause of death in intensive care units, with a mortality rate in excess of 50%. The outcome is determined not only by the infection but also by the intensity of the immuno-inflammatory response. This response is essential for the resolution of infection but may occur in an uncontrolled manner causing damage to the host. The pronounced synergy and interaction of the components of the immune system dictate that modulation may result in either immunostimulation or immunosuppression. Coordination of the host immune response to infection and inflammation in terms of expression of the effector molecules is vital to an optimum response (Fig. 1).

Innate and acquired immunity

Mediators of immunity and inflammation (families of protein and lipid molecules) are part of an intercellular signalling language which allows cells/tissues/organs to take in new information and, based on past experience, decide what to do next. There are essentially two components to the immune response—innate (non-specific) and acquired (antibody-mediated) immunity.

The body possesses a range of barriers to prevent micro-organisms from entering, including the skin, mucous secretion, ciliary action and gastric acid. If these barriers are crossed micro-organisms are destroyed by soluble factors such as lysozyme and by phagocytosis with intracellular digestion (termed innate immunity). The complement system is a multi-component triggered enzyme cascade which attracts phagocytes to micro-organisms increasing capillary permeability and neutrophil chemotaxis and adhesion. Specific acquired immunity in the form of antibodies inactivates micro-organisms which are not destroyed by the innate immune system. Such micro-organisms either fail to activate the complement pathway or prevent activation of phagocytes. The cells involved in innate immunity include "professional" phagocytes (polymorphonuclear neutrophils, mast cells and macrophages) and "non-professional" phagocytes (endothelial cells and hepatocytes). Cells infected with viruses and parasites are killed by large granular lymphocytes termed natural killer (NK) cells, and eosinophils.

Acquired immune defences against specific micro-organisms (antigens) form the second component of the immune response. Antibodies activate the complement system, stimulate phagocytic cells and specifically inactivate micro-organisms. Lymphocytes, the basis of the acquired immune defence system, consist of antibody-producing plasma cells derived from B-lymphocytes, and T-lymphocytes which control intracellular infections. Binding of micro-organisms to antibodies on the cell surface of B-cells leads to preferential selection of these antibody-producing cells. This is termed priming, and subsequent responses are faster and amplified, and provide the basis of vaccination. T-cells exploit two main strategies to combat intracellular infections—secretion of soluble mediators which activate other cells to enhance microbial defence mechanisms, and production of cytolytic T-cells which kill the target organism. Adaptive selection of specific T-cell subsets occurs in response to local balance of cytokine concentrations [12].

Cytokines

Orchestration of immune and inflammatory responses depends upon communication between cells by soluble molecules given the generic term cytokines, including chemokines, interleukins (IL), growth factors and interferons (IFN). They are low molecular weight secreted proteins which regulate both the amplitude and duration of the immune/inflammatory responses (table 1). They have a transient action which is tightly regulated. Cytokines are highly active at very low concentrations, combining with small numbers of high affinity cell surface receptors and producing changes in the patterns of RNA and protein synthesis. They have multiple effects on growth and differentiation in a variety of cell types with considerable overlap and redundancy between them, partially accounted for by the induction of synthesis of common proteins. Interaction may occur in a cascade system in which one cytokine induces another, through modulation of the receptor of another cytokine and through either synergism or antagonism of two cytokines

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Key words

Immune response. Proteins, cytokines. Complications, infections.

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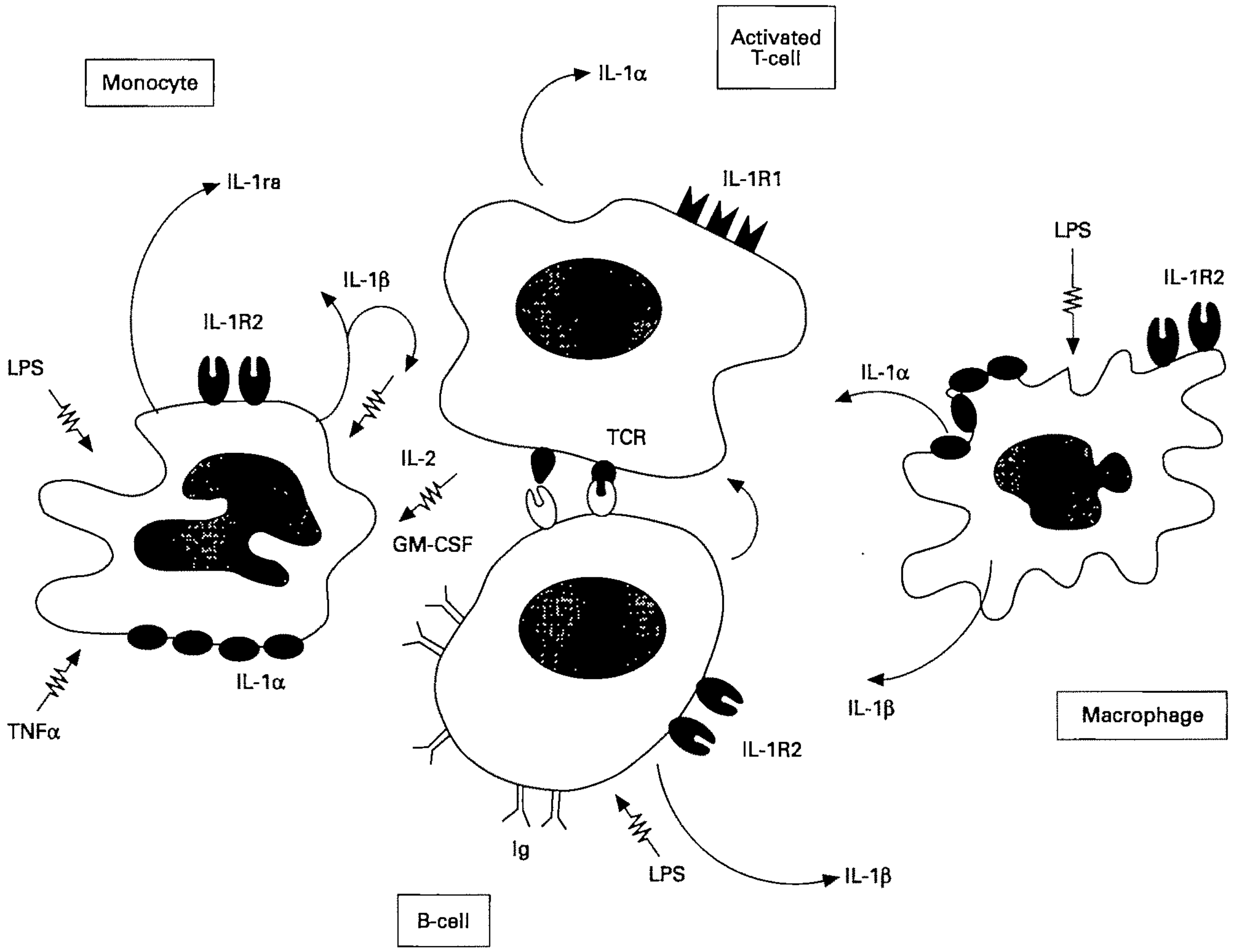

Figure 1 Schematic diagram showing the interaction between monocytes, macrophages, activated T-cells and B-cells during the immuno-inflammatory response. (GM-CSF, granulocyte-macrophage colony stimulating factor; Ig, immunoglobulin; IL-1α, interleukin 1α; IL-1β, interleukin 1β; IL-1ra, interleukin 1 receptor antagonist; IL-1R1, interleukin 1 receptor type I; IL-1R2, interleukin 1 receptor type II; IL-2, interleukin 2; LPS, lipopolysaccharide; TCR, T-cell receptor; TNFα, tumour necrosis factor α.)

acting on the same cell. Cytokines should not be considered as having identifying labels for being growth stimulators or inhibitors and pro- or anti-inflammatory actions. Their specific actions depend on the stimulus, the cell type and the presence of other mediators and receptors.

Chemokines are a family of small, pro-inflammatory molecules characterized by four conserved cysteine residues. The α-chemokines have two pairs of cysteine residues separated by a variable amino acid and chemoattract neutrophils (e.g. interleukin 8, platelet basic protein, epithelial neutrophil activating peptide) whereas β-chemokines have two adjacent pairs of cysteine groups and are chemotactic for monocytes/macrophages (e.g. platelet factor 4, monocyte chemotactic protein 1, macrophage inflammatory protein 1) and T-cells (e.g. RANTES). Chemokines have been described as having more restricted actions than cytokines, but this is more likely to be the result of differential expression of receptors [9]. Interferons (IFN α, β, γ) are a family of broad spectrum antiviral agents which also modulate the activity of other cells, particularly IL-8 and platelet activating factor (PAF) production, antibody production by B-cells and activation of cytotoxic macrophages [5]. Growth factors regulate the differentiation, proliferation, activity and function of specific cell types [17]. The best known are colony stimulating factors which cause colony formation by haematogenic progenitor cells (e.g. granulocyte-macrophage colony stimulating factor or GM-CSF). Other examples include factors which regulate the growth of nerve cells, fibroblasts, epidermis and hepatocytes.

In addition to the low molecular weight protein mediators, there are also lipid mediators of inflammation which include PAF and arachidonic acid metabolites. Platelet activating factor is a labile alkyl phospholipid released from a variety of cells in the presence of antigen and leucocytes in response to immune complexes. In addition to its platelet effects, the actions of PAF include the priming of macrophages to other inflammatory mediators and alterations of microvascular permeability [11]. Arachidonic acid metabolites include the prostaglandins, leukotrienes, HETE and HPETE, all of which have profound inflammatory and vascular actions, and may regulate and be regulated by, other cytokines.

Tumour necrosis factors (TNF) α and β have a vast range of similar effects and are usually referred to as inflammatory cytokines [2]. They have a central role in initiating the cascade of other cytokines and factors that make up the immune response to infection. The wide variety of effects is attributable to the ubiquity of their receptors, their ability to activate multiple signal transduction pathways and their ability to induce or suppress an array of genes including those for growth factors, cytokines, transcription factors, receptors and acute phase proteins. Although both TNFs have similar biological activities, regulation of the expression and processing of the two is quite different.

Control of adaptive T-cell selection

The major histocompatibility complex (MHC) includes genes encoding class I and II cell surface glycoproteins whose function is to present antigenic peptides to T-cells. Regulation of MHC gene expression, e.g. by cytokines (table 1), plays a fundamental role in the immune system, since alterations of cell surface expression of class I or II molecules can affect the efficiency of antigen presentation. T-lymphocytes consist of two subsets: T helper (Th)-cells which recognize class II MHC molecules and which produce IFNγ and other macrophage-activating factors; cytotoxic or killer T-cells which recognize both specific antigens and class I MHC molecules on the surface of infected cells.

Circulating Th-cells are capable of unrestricted cytokine expression and are prompted into a more restricted and focused pattern of cytokine production depending on signals received at the outset of infection [12]. Th-cells can be classified according to the pattern of cytokines they produce. Th1 category cells secrete a characteristic set of cytokines which push the system towards cellular immunity (cellular cytotoxicity). Th2-cells are associated with humoral or antibody-mediated immunity. Typically Th1-cells secrete IL-2, IFNγ, TNFβ and transforming growth factor β (TGFβ) whereas the Th2-cells secrete IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 and also help B-cell antibody production. Both cell types produce IL-3, TNFα and GM-CSF. Interleukins 12 and 4 have been identified as early inducers of Th1 and Th2 responses respectively, and therefore the local balance of these cytokines is an important determinant of subsequent immune responses. Understanding the influence of antigen-independent cytokine production on the subsequent acquisition of adequate immune responses to an infection is clearly important.

Receptors and antagonists

The biological activities of cytokines are regulated by specific cellular receptors. Often these receptors comprise multiple subunits providing phased stages of activation and biological action. For example, the IL-2 receptor complex consists of three subunits, IL-2Rα, IL-2Rβ and IL-2γ. Although the IL-2Rα/β combination can bind IL-2, IL-2Rγ is also required for high affinity binding, ligand internalization and signalling which are required for maximal effect [14]. Other cellular receptors exist in more than one type which act alone but have different binding affinities for different forms of a cytokine protein (e.g. IL-1 receptor type I binds IL-α better than IL-1β, and IL-1 receptor type II has more affinity for IL-β). Binding of a cytokine to one type of receptor may result in interactions with another receptor; the two receptors for TNF, for example, use ligand passing in which TNF binds transiently to receptor type I, with full signal transduction, but may then move onto the type II receptor with activation of another signal for apoptosis or programmed cell killing [20].

Soluble cytokine receptors have been identified which compete with membrane-bound receptors, thus regulating cytokine signals. Exceptions to this are soluble receptors for IL-6 and ciliary neurotrophic factor which act as agonists rather than antagonists [19]. Such soluble receptors may be membrane-bound receptors which are shed into the circulation either intact or as truncated forms (e.g. soluble TNF receptors, sTNF-R), or may begin as related precursor molecules which are enzymatically cleaved (e.g. IL-1R). Soluble receptors may appear in response to stimuli as part of a naturally occurring independent regulatory process to limit the deleterious effects of a mediator (e.g. sTNF-R), but some soluble receptors have little binding activity and may represent superficial and unimportant losses of cellular receptors (e.g. the soluble form of the IL-2Rα). Soluble cytokine receptors not only mediate biological activity but control desensitization to ligands by reduced availability, decreased signalling and by stimulating cellular mechanisms which can result in lack of activity.

The biological actions of some cytokines are also regulated by receptor antagonists. The receptor antagonist for IL-1 (IL-1ra) competes with cell receptors for IL-1, but when bound does not induce signalling. IL-1ra binds to cell receptors much more avidly than to soluble receptors, such that soluble receptors will have little effect of the inhibitory action of the receptor antagonist. The soluble receptor also inhibits activation of the pro-IL-1β precursor. The appearance of IL-1ra is independently regulated by other cytokines as part of the inflammatory process [4].

Mechanisms of multi-organ failure

Severe infection leads to the appearance of endotoxin or lipopolysaccharide (LPS) in the bloodstream which triggers the innate immune responses such as activation of phagocytic cells and activation of the alternative complement cascade, leading to the production of the primary pro-inflammatory mediators, TNF and IL-1. Secondary mediators including other cytokines, prostaglandins and PAF are then released, with further activation of complement and the acute phase response, expression of adhesion molecules, T-cell selection, antibody production and release of oxygen-derived radicals [3, 7, 21]. Other toxins and cellular debris must also trigger such a systemic inflammatory response, since this process occurs in the absence of LPS release.

Local effects of the inflammatory response are essential for the control of infection. Prolonged systemic exposure to high concentrations of cyto-

Table 1 Sources and biological effects of the immune mediators (ARDS, acute respiratory distress syndrome; GM-CSF, granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte-colony stimulating factor; IFN, interferon; IgA, immunoglobulin A; IgG, immunoglobulin G; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; MHC, major histocompatibility complex; mRNA, messenger RNA; NK, natural killer cells; NO, nitric oxide; NOS, nitric oxide synthase; ODFR, oxygen-derived free radicals; PAF, platelet activating factor; Pg, prostaglandin; TGF, transforming growth factor; TNF, tumour necrosis factor.)

Mediator	*Source*	Biology activity	*Effects on other cells*
IFNα IFNβ	T-cells B-cells Macrophages Fibroblasts	Pyrogenic; cytotoxic.	Macrophages (increases class I MHC antigens, IL-1, PAF production); B-cells (proliferation, differentiation); T-cells (proliferation); chemotactic.
IFNγ	T-cells NK cells	Pyrogenic; antiviral; cytotoxic; anti-tumour effect; mimics septic shock; causes release of NO and ODFRs; and upregulates IL-1 and PAF production	Macrophages (increases class I MHC antigens, IL-1, PAF production, downregulates IL-2 mediated IL-8 mRNA); B-cells (proliferation and differentiation); chemotactic for monocytes; stimulates formation of adhesion molecules.
TNFα	Neutrophils Lymphocytes NK cells Endothelial cells Smooth muscle cells	Pyrogenic; cytotoxic; anti-tumour effect; mimics septic shock; promotes angiogenesis; causes release of NO and ODFRs; induces or suppresses gene expression for cytokines, receptors and acute phase proteins.	Wide variety of effects due to ability to mediate expression of genes. Important role in host resistance to infection as immuno-stimulant and mediator of the inflammatory response. Promotes haematopoiesis. Important role in intercellular communication.
IL-1	Macrophages Endothelial cells Fibroblasts Hepatocytes	Pyrogenic; cytotoxic; anti-tumour effect; promotes angiogenesis; causes release of NO and ODFRs; induces prostaglandin synthesis; initiates the acute phase response.	Macrophages (TNF and IL-6 production); B-cells (proliferation, differentiation; T-cells (proliferation) chemotaxis; formation of adhesion molecules; haematopoiesis.
IL-2	T-cells	Pyrogenic; anti-tumour effect; mimics septic shock; causes release of ODFRs.	B-cells and T-cells (proliferation, differentiation, release of IgG from activated B-cells); chemotaxis; augments neutrophil and macrophage function; formation of adhesion molecules.
IL-4	T-cells B-cells Macrophages	Cytotoxic; anti-tumour effect; inhibits induction of nitric oxide synthase; inhibits release of superoxide by macrophages; numerous anti-inflammatory effects.	Macrophages (suppresses activation, upregulates class II MHC antigens, inhibits IgG receptor expression, inhibits expression of IL-1, IL-6, IL-8, TNF, stimulates IL-1ra expression); B-cells and T-cells (proliferation, differentiation, enhances antigen-presenting capacity); chemotaxis; formation of endothelial cell adhesion molecules; haematopoiesis.
IL-6	T-cells Macrophages Endothelial cells Fibroblasts Hepatocytes	Cytotoxic; anti-tumour effect; mimics septic shock; causes release of ODFRs; induces hepatic acute phase proteins	B-cells (differentiation, antibody production); T-cells (activation, proliferation, differentiation, induces IL-2 production); formation of adhesion molecules; haematopoiesis.

kines and other components of the immuno-inflammatory cascade may contribute to the development of MODS. Damage and activation of the endothelium, which plays a pivotal role in the regulation of haemostasis, vascular tone and fibrinolysis, have profound consequences. The endothelium produces several substances which regulate inflammation and regional perfusion, including nitric oxide, vasoactive arachidonic acid metabolites and cytokines [18]. Changes in the balance of concentrations of these substances may contribute to the pathogenesis of the inflammatory response during sepsis and injury. Phagocytic cells are in constant contact with the endothelium and disturbance of the relationship between these two cell types may result in direct tissue damage as a result of local production of oxygen-derived free radicals, hypochlorous acid and proteolytic enzymes. Another hypothesis to explain the observed tissue damage and organ dysfunction is that of local tissue ischaemia and hypoxia as a result of microthrombi formed by a coagulopathy or platelet or white cell aggregates. There is evidence for all of these mechanisms and it is probable that the pathogenesis of MODS and organ failure is diverse and complex and is unlikely to be attributable to a single mechanism.

Potential for therapy

Both soluble receptors and monoclonal antibodies directed against receptors can be used to block the interaction of a cytokine with its receptor. This then prevents transduction of the appropriate biological signal in the target cell. The cloning of genes encoding cytokine receptor chains and the characterization of their soluble forms has resulted in new approaches to anti-cytokine therapy. Injection of a recombinant soluble receptor might prevent the deleterious effect of excessive cytokine production. In addition to soluble receptors, monoclonal antibodies which block cellular cytokine receptors can be used as anti-cytokine therapy. However, these small

Table 1—(cont.)

Mediator	*Source*	Biology activity	*Effects on other cells*
IL-8	T-cells Macrophages Endothelial cells Hepatocytes Neutrophils Fibroblasts	Angiogenic; leucocyte infiltration in septic shock and ARDS.	Neutrophils (activation); upregulates cell adhesion molecules; chemotactic for PMNs.
IL-10	T-cells B-cells Macrophages	Inhibits induction of nitric oxide synthase; suppresses synthesis of ODFRs; may be immunostimulatory or immunosuppressive.	Macrophages antigen presenting capacity, downregulates class II MHC antigen expression, suppresses PgE2, TNF, IL-1, IL-6, IL-8 production); B-cells (induces IgA synthesis, enhances survival, upregulates IL-2 receptors); T-cells (inhibits IFNγ); neutrophils (inhibits pro-inflammatory cytokine synthesis, upregulates IL-1ra expression).
G-CSF	Macrophages Endothelial cells	Proliferation, differentiation and activation of neutrophils; mimics septic shock; causes release of ODFRs.	Neutrophils (proliferation, prolongs survival, enhances antibody dependent cytotoxicity and superoxide anion production); chemotactic for granulocytes and monocytes.
GM-CSF	T-cells B-cells Macrophages Endothelial cells Fibroblasts	Proliferation, maturation and function of haematopoietic cells; causes release of ODFRs.	Neutrophils (proliferation, differentiation, prolongs survival, increases superoxide, leukotriene, PAF, arachidonic acid release, enhances phagocytic activity, inhibits IL-8 production and neutrophil migration); monocytes (proliferation, differentiation, induces IL-1, IL-8 and TNF release); chemotaxis; formation of adhesion molecules; angiogenesis; haematopoiesis.
TGFβ	Platelets Fibroblasts Monocytes	Stimulatory or inhibitory effects on proliferation and differentiation of many cell types depending on type of cell, growth conditions, cell differentiation state, and presence of other growth factors; modulates cellular and humoral immune responses; suppresses chemokine-mediated NO release.	Lymphocytes (suppresses B and T-cell proliferation, inhibits NK activity, inhibits IgG and IgM secretion, upregulates B-cell IgA secretion); macrophages (induces secretion of growth factors); chemotactic for macrophages.
IL-1ra	Macrophages Endothelial cells Neutrophils Fibroblasts	Blocks the biological activity of IL-1 by competing for the IL-1 by competing for the IL-1 receptor.	
PAF	Macrophages Endothelial cells Neutrophils	Activates and aggregates platelets; mimics endothelial alterations of septic shock; induces release of ODFRs.	Macrophages (enhances IL-1, IL-2 and TNF production); intracellular messenger in neutrophils; causes release of lysosomal enzymes; chemotactic for neutrophils; formation of adhesion molecules.

molecules have short half-lives and therefore derivatized molecules with longer half-lives and higher affinity have now been developed. However, it has been shown that cytokine complexed to such binding proteins is still available for receptor binding [10]. It is possible that these complexes can still act as agonists *in vivo* depending on concentrations of other mediators and relative receptor expression. Another approach to minimizing the deleterious effects of the uncontrolled inflammatory process is to blunt the final common pathways of damage (i.e. using either agents which decrease free radical production or antioxidants which inactivate free radicals as they are produced).

Monoclonal antibodies to TNFα have been used both in clinical and animal studies [22]. The use of sTNF receptors has also been evaluated in sepsis [1, 23]. The naturally occurring IL-1 receptor antagonist has been studied in two large clinical trials [15]. It is also possible to modulate the production of TNF at the mRNA level using pentoxyphylline, and there have been several promising animal studies [8]. Specific chemical antagonists, for example against PAF, have also been evaluated in patients with sepsis.

Blockade of any single or combined inflammatory mediator may not be successful for a number of reasons. First, the immuno-inflammatory process is a normal response to infection and is essential not only for the resolution of infection but also for the initiation of other adaptive stress responses required for host survival (e.g. acute phase and heat shock responses) [16]. Second, the profound redundancy of action of many cytokines means that there are many overlapping pathways for cellular activation and further mediator release. In addition, the synergism of actions and effects of many cytokines suggests that imbalance in the process of the immune response may be adversely affected by inhibition of a single agent. We also suggest that exogenously administered anti-cytokine therapy may have hitherto unrecognized effects caused by interaction with naturally occurring immunomodulators or their receptors [10]. Finally, the timing of any potential anti-cytokine therapy is clearly crucial [24]. Strategies designed to predict the activation of specific components of the inflammatory response may thus be useful. It is also possible that specific cellular targeting of such therapy may be more beneficial than global inhibition. Preliminary animal studies suggest that the therapeutic use of anti-inflammatory cytokines such as IL-10 and IL-13 may be beneficial in sepsis although as yet there have been no confirmatory clinical studies [6, 13].

References

1. Ashkenazi A, Marsters SA, Capon DJ, Chamow SM, Figari IS, Pennica D, Goeddel DV, Palladino MA Jr, Smith DH. Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin. *Proceeding of the National Academy of Sciences USA* 1991; **88**: 10535–10539.
2. Beutler B, Greenwald D, Hulmes JD. Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. *Nature* 1985; **316**: 552–554.
3. Cowley HC, Heaney D, Gearing A, Webster NR. Increased circulating adhesion molecule concentrations in patients with the systemic inflammatory response syndrome: a prospective cohort study. *Critical Care Medicine* 1994; **22**: 651–657.
4. Dripps DJ, Brandhuber BJ, Thompson RC, Eisenberg SP. Interleukin 1 (IL-1) receptor antagonist binds to the 80kDa IL-1 receptor but does not initiate IL-1 signal transduction. *Journal of Biological Chemistry* 1991; **266**: 10331–10336.
5. Farrar MA, Schreiber RD. The molecular biology of interferon-gamma. *Annual Review of Immunology* 1993; **11**: 571–611.
6. Gerard C, Bruyns C, Marchant A, Abramowicz D, Vasndenabeele P, Delvaux A, Fiers W, Goldman M, Velu T. Interleukin 10 reduces the lethality of tumour necrosis factor and prevents lethality in experimental endotoxemia. *Journal of Experimental Medicine* 1993; **177**: 547–550.
7. Goode HF, Webster NR. Free radicals and antioxidants in sepsis. *Critical Care Medicine* 1993; **21**: 1770–1776.
8. Han J, Thompson P, Beutler B. Dexamethasone and pentoxyfylline inhibit endotoxin induced cachectin/TNF synthesis at separate points of the signalling pathway. *Journal of Experimental Medicine* 1990; **172**: 391–394.
9. Horuk R.The interleukin 8 receptor family: from chemokines to malaria. *Immunology Today* 1994; **15**: 169–173.
10. Klein B, Braily H. Cytokine binding proteins: stimulating antagonists. *Immunology Today* 1995; **16**: 216–220.
11. Koltai M, Hosford D, Guinot P, Esanu A, Braquet P. PAF: a review of its effects, antagonists and possible future clinical implications. *Drugs* 1991; **42**: Part I 9–29, Part II 174–204.
12. Kuchroo VK, Das MP, Brown JA, Ranger AM, Zamvil, SS, Sobel RA, Wiener HL, Nabavi M, Glimcher LH. B7-1 and B7-2 co-stimulatory molecules activate differentially the Th1/Th2 developmental pathways. *Cell* 1995; **80**: 707–718.
13. Minty A, Chalon P, Derocq JM, Dumont X, Guillemot JC, Kaghad M, Labit C, Leplatoit P, Liauzun P, Miloux B. Interleukin 13 is a new human lymphokine regulating inflammatory and immune responses. *Nature* 1993; **362**: 248–250.
14. Nelson BH, Lord JD, Greenberg PD. Cytoplasmic domains of the interleukin 2 receptor beta and gamma chains mediate the signal for T-cell proliferation. *Nature* 1994; **369**: 333–336.
15. Ohlsson K, Bjork P, Bergenfeldt M. Interleukin 1 receptor antagonist reduces mortality from endotoxin shock. *Nature* 1990; **348**: 550–552.
16. Perlmutter DH, Dinarello CA, Punsal PI, Cohen HR. Cachectin/tumour necrosis factor regulated hepatic acute phase gene expression. *Journal of Clinical Investigation* 1986; **78**: 1349–1354.
17. Pimental E. *Handbook of Growth Factors*, Volume III, Boca Raton: CRC Press, 1994.
18. Redi H, Schlag G, Marzi I. Leucocyte endothelial interactions in trauma and sepsis. In: Lamy M, Thijs LG, eds. *Mediators of Sepsis*. Berlin: Springer-Verlag, 1992; 124–135.
19. Rose-John S, Heinrich PC. Soluble receptors for cytokines and growth factors: generation and biological function. *Biochemical Journal* 1994; **300**: 281–290.
20. Tartaglia LA, Pennica D, Goeddel DV. Ligand passing: the 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signalling by the 55-kDa TNF receptor. *Journal of Biological Chemistry* 1993; **268**: 18542–18548.
21. Thijs LG, Hack CE. Role of the complement cascade in severe sepsis. In: Lamy M, Thijs LG, eds. *Mediators of Sepsis*. Berlin: Springer-Verlag, 1992; 78–98 .
22. Tracey K, Fong Y, Hesse DG. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 1987; **330**: 662–664.
23. VanZee KJ, Kohno T, Fischer E, Rock CS, Moldawer L, Lowry SF. Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor alpha in vitro and in vivo. *Proceedings of the National Academy of Sciences USA* 1992; **89**: 4845–4849.
24. Webster NR on behalf of the Intersept Study Group. Intersept: An international efficacy and safety study of monoclonal antibody (Mab) to human tumour necrosis factor in patients with the sepsis syndrome. *Clinical Intensive Care* 1995; **6**: S81.

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Disturbance of leucocyte circulation and adhesion to the endothelium as factors in circulatory pathology

D. H. ADAMS AND G. B. NASH

Advances in molecular biology have given us the tools to dissect the mechanisms which control the circulation of leucocytes. In particular, a sequence of intermolecular adhesive interactions has been described which underlies leucocyte attachment to the vessel wall, and the factors which promote and limit these interactions have begun to be appreciated. These discoveries have led to a rekindling of interest in the inflammatory response arising from extravasation of neutrophils and to a growing understanding of the basis of lymphocyte recirculation and targeting to specific organs [9, 72, 97]. Much work has been based, of necessity, on *in vitro* model systems, but animal studies and intravital techniques have enabled the molecular concepts to be tested, so that there is growing confidence that they are indeed the basis of physiological and pathological processes. Multiple organ failure (MOF) is attended by disturbance of tissue perfusion and degradative damage associated with an extreme inflammatory response, which may arise, in part at least, from a loss of the normal mechanisms controlling leucocyte circulation and migration into tissue [109]. It is thus our aim to review the circulatory and adhesive behaviour of leucocytes (especially neutrophilic granulocytes or neutrophils), along with its molecular basis and control mechanisms, and to evaluate the evidence that disruption of the normal physiological processes contributes to pathologies such as MOF.

Circulation of leucocytes

LIFESPAN, CIRCULATION AND RHEOLOGY

Although a large proportion of mature leucocytes are circulating at any given time, their physiological function is not carried out in the vascular compartment. Thus, neutrophils circulate for about 7–10 h on average before migrating into tissue as part of an inflammatory response where they phagocytose and destroy foreign bodies and necrotic tissue. The neutrophils found in the systemic blood represent only about 50 % of the circulating pool, so that there is a marginated population travelling slowly through the lungs and microcirculation which can be mobilized rapidly, for example by exercise or catecholamines [12]. Monocytes circulate for a similar period, but then become resident in tissues as macrophages for a period up to months, acting as a potent source of mediators such as cytokines, and forming an active part of the phagocytic reticuloendothelial system in the spleen, liver and bone marrow. Lymphocytes have a more complex pattern of behaviour, because they are the only leucocytes that return to the blood via the lymphatic system after migration into tissue (i.e. recirculation; see Ager [19] for review). The tissue to which they migrate depends on their subtype and activation status (see below).

The transformation from a circulating leucocyte to a non-circulating or migrated leucocyte depends on changes in the cellular rheological properties of resistance to mechanical deformation and adhesiveness. Successful passage through the microcirculation is dependent on the deformability of the leucocytes (because capillary diameter is often less than the cell dimensions) and on maintenance of a non-adhesive response to the endothelium. As is made evident below, the endothelial cells lining the microvessels, particularly on the venous side, are not passive partners in the potential adhesive interaction. At this stage it is sufficient to realize that it is disturbance in the balance of physical forces which determines whether or not a cell becomes immobilized in the microcirculation (i.e. circulatory driving force *vs* resistance to deformation or *vs* adhesive interaction). In the "physiological" response, controlled adhesive interactions enable leucocytes to attach to the vessel wall, and modulation of cellular mechanical properties allows locomotion and migration into tissue. However, uncontrolled changes in adhesive or cellular mechanical properties or in circulatory forces may lead to trapping in microvessels that could be "pathological".

MECHANICAL FAILURE TO CIRCULATE—A CONTRIBUTOR TO CIRCULATORY DISORDER?

Outside of severely hyperleucotic leukaemias, it is generally considered that leucocytes do not contribute to the bulk flow resistance of the blood in large vessels. However, although outnumbered by red cells by about 700:1, leucocytes can contribute to the resistance to flow and distribution of flow in

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Key words
Blood, leucocytes. Blood, flow.

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microvessels [38]. This is because the intrinsic resistance to flow into a small capillary is about 1000-fold greater for a leucocyte than a red cell [28]. Thus, it has been recognized from intravital observations, including those made in humans, that even normal leucocytes travel very slowly into capillaries, have the ability to hold up "trains" of red cells and can cause stop–go flow in individual capillaries [13, 14]. This seems to apply to each class of leucocyte, although all evidently negotiate the microcirculation successfully in the steady state. Problems may arise, however, if perfusion pressure is reduced or if neutrophils, in particular, become activated.

Studies in animal models show that reduction of perfusion pressure, induced artificially or after shock, leads to plugging of capillaries by leucocytes and increase in flow resistance [13]. Moreover, the return of driving pressure to normal does not seem to enable perfusion to be completely recovered. A similar series of events follows arterial ligation, for instance in animal models of myocardial infarction [33]. It appears that initial trapping of "normal" leucocytes may be mechanical, but that a process of activation ensues for neutrophils, probably prompted by mediators released in the affected tissue (e.g. activated complement, eicosanoids or endothelial-derived factors such as interleukin 8 (IL-8) or platelet-activating factor (PAF)). Activation causes rapid rigidification of neutrophils because of the formation of actin polymer in the cytoplasm [34] and also increases their adhesive potential (see below). Actin polymerization is the motor for migration of leucocytes into tissue, but if stimulated at an inappropriate time it will inhibit their circulation. Adhesion, as well as enabling extravascular migration, may also promote vascular occlusion. Such activation-induced changes in mechanical and adhesive properties will tend to stop cells from being dislodged after return of perfusion pressure. Not only this, but reperfusion brings new leucocytes to the tissue, which are in turn activated by mediators and change their mechanical and adhesive properties [85]. Thus there is the potential for a vicious cycle of increasing vascular blockage followed by tissue damage arising from the lytic enzymes and oxidants known to be released by activated neutrophils (fig. 1) [64, 106].

That such a process follows ischaemic and inflammatory events has been demonstrated in animal models [13, 85, 107] and is evidenced in humans by findings of systemic activation of neutrophils and changes in their mechanical properties [62, 64, 65]. Thus, it may be that circulatory obstruction occurs locally in an "insulted" tissue but also becomes disseminated because of release of activated cells (e.g. those which do not respond rapidly enough to be trapped locally), stimulatory mediators, or both. Such mediators may act on circulating neutrophils and also on remote endothelial cells to change their adhesive properties (see below). The lung may act as a filter of activated cells because of its low perfusion pressure and peculiar microvascular structure, where cells must pass through a series of capillary segments without shunting. The basis of trapping might be mechanical, adhesive, or both, although animal studies suggest that mechanical changes alone can be sufficient [112]. Other organs, such as the spleen, liver and kidney may also be susceptible because of structural features which promote trapping of rigid cells. The mechanical factors likely to influence the sites of microvascular entrapment of leucocytes are summarized in figure 2.

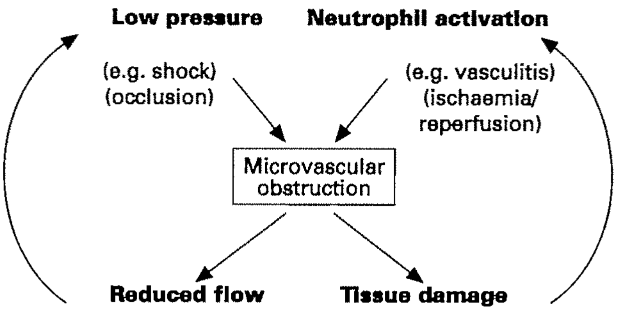

Figure 1 Mechanisms of obstruction of microvessels by neutrophils and the potential for feedback and establishment of a vicious cycle. If driving pressure is insufficient, neutrophils may become mechanically lodged in capillaries, leading to a further reduction in flow. Activation of neutrophils may cause trapping even at normal perfusion pressure, and the localized cells may induce vascular damage and release of mediators causing a second wave of activation.

CONSTRAINTS PLACED ON ADHESION BY CIRCULATION

Another important implication of circulatory dynamics and forces is that they impose constraints on the adhesive processes underlying leucocyte–endothelial interaction [45]. Leucocytes appear to adhere mainly in post-capillary venules where their velocities are relatively low but still of the order of hundreds of μm s^{-1}. Given the dimensions of the interacting cells and of the adhesion molecules on their surface, it is clear that individual molecular interactions have to be rapid to make the chance of capturing a cell finite. It has thus been realized that it is the kinetics of intermolecular adhesive interactions that are important (i.e. the "on-rates" relative to the flow rate, rather than the equilibrium affinity constants) in limiting cell capture [108]. Once adhesive bonds have formed, then they are put under stress by the fluid drag acting on the now stationary cell. These forces tend to break the bonds, and so capture might be followed by detachment, unless stabilizing bonds are formed rapidly. Alternatively, cells may roll slowly along the surface after capture because they are able to form new bonds at the front while bonds "peel" at the rear of the cell [104]. In addition, migration after stabilization implies that cells can unstick and re-stick themselves as they move, with flow forces acting on them continually until they have exited the vessel lumen. It would seem unlikely *a priori* that a single type of receptor–ligand interaction could have the necessary physical characteristics to support all stages of such a process in a controlled manner. Indeed molecular specialization appears to have been evolved in order to overcome this problem, and is described in the next section, along with our current understanding of how leucocyte adhesion to endothelium is achieved.

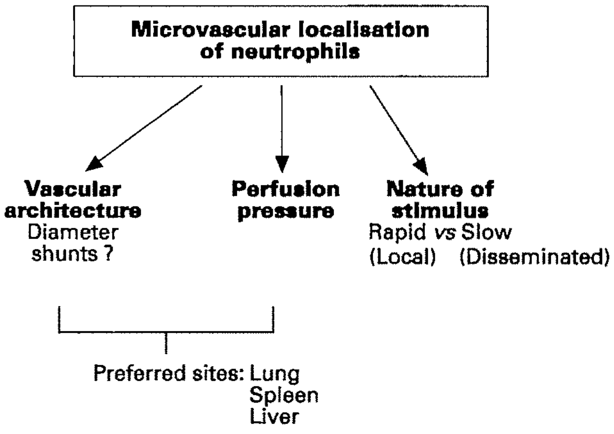

Figure 2 Factors influencing the site of mechanical trapping of neutrophils in tissue. Cellular resistance to flow is greatly dependent on vessel diameter [25], so that organs with narrow capillaries or sinusoidal structure, and with vascular architecture lacking shunts will be likely to filter cells, especially if the perfusion pressure is low (e.g. in the lungs). The same factors apply for rigidified neutrophils after activation, but if the mechanical response after activation is rapid, cells may be trapped in the tissue where the stimulus originated, while a slow response will lead to dissemination of the cells in the circulation.

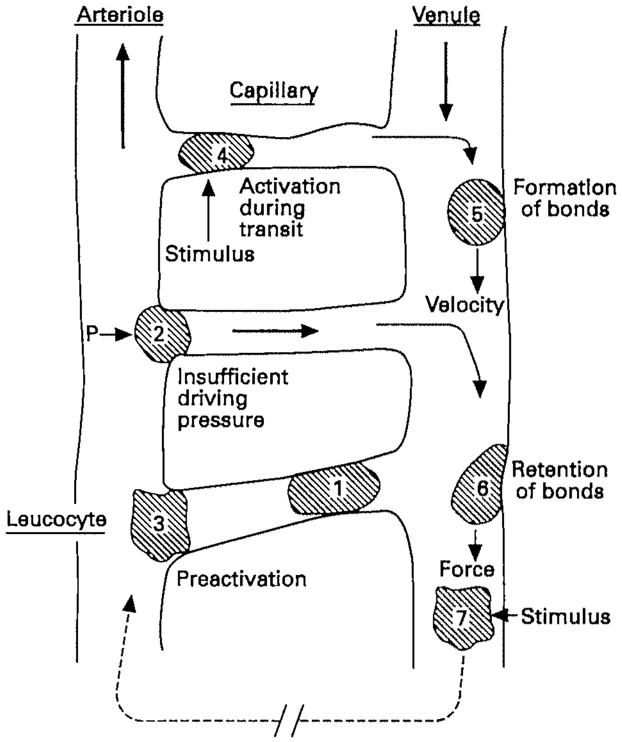

Figure 3 Mechanical factors affecting circulation of leucocytes passing from arterioles to capillaries to venules. Cells may need to undergo marked deformation and elongation to pass through capillaries (1), and may be unsuccessful if the perfusion pressure is reduced (2) or if they are activated by systemic (3) or local stimuli (4). Cells may adhere to venules if they can form bonds rapidly enough compared with flow rate (5) and if adhesive bonds can withstand shear forces (6). Cells failing to attach when stimulated (7) and released into the blood may be systemically active.

Figure 3 summarizes the role of physical forces in the microcirculation: leucocytes continue to circulate given adequate perfusion pressure, but if this driving force is reduced or if cells are activated by local or systemic inflammatory mediators, then inability to pass through capillaries may induce immobilization. Immobilization also arises from adhesive interaction with the vessel wall, dependent on the velocity of motion before capture and on the shear forces acting against subsequent stable attachment.

Leucocyte migration and recirculation

Leucocytes migrate extensively throughout the body to maintain immune surveillance and to mount rapid inflammatory responses to invading pathogens [6]. Different leucocytes have particular patterns of migration that are suited to their functional capacities. For instance, as mentioned above, neutrophils are a population of relatively simple effector cells that form an early response to infection or injury. They are rapidly recruited in large numbers to sites of inflammation where they are activated to release their intracellular contents. This activation is provided by general mechanisms and is not dependent upon the precise structure of the offending antigen, i.e. it is antigen-independent. Neutrophils do not recirculate and once they have entered tissue they either die by activation and release of cytoplasmic contents or they are removed by phagocytic macrophages.

T-lymphocytes, on the other hand, are a highly sophisticated population of cells, that are activated by specific antigens to which they have been programmed to respond. In most circumstances T-lymphocytes are recruited later and more selectively than neutrophils to diverse sites of inflammation. In contradistinction to neutrophils, T-cells have the ability to return to the circulation via the lymphatics. This permits them to recirculate through normal tissue and provide ongoing immune surveillance [72]. Their ability to respond to specific foreign peptides allows them to mount a highly selective response to invading foreign antigens [20, 99]. Naive T-cells (those that have not been exposed to antigen) recirculate almost entirely through lymphoid tissue where they are most likely to encounter their specific antigen in the specialized environment of the lymph node where optimal antigen presentation and activation can occur. However, after exposure to antigen in lymphoid tissue the naive T-cell returns to the resting state as a memory cell, primed to respond rapidly to a second encounter with antigen. In order to enhance its chances of re-encountering its specific antigen the memory T-cell recirculates preferentially through the tissue in which it was originally exposed to antigen [6, 72].

These subtle patterns of recirculation can be overcome in inflammation where release of pro-inflammatory factors results in the recruitment of a wider range of cell types. The composition of an inflammatory infiltrate will depend upon the nature of the pathogenic stimulus; for instance, the infiltrate of an allergic reaction may contain large numbers of eosinophils whereas T-cells and macrophages predominate in graft rejection and neutrophils at sites of acute bacterial sepsis. Furthermore, the inflammatory infiltrate changes over time, for instance an initial type I hypersensitivity reaction will provoke an influx of mast cells and eosinophils which will be

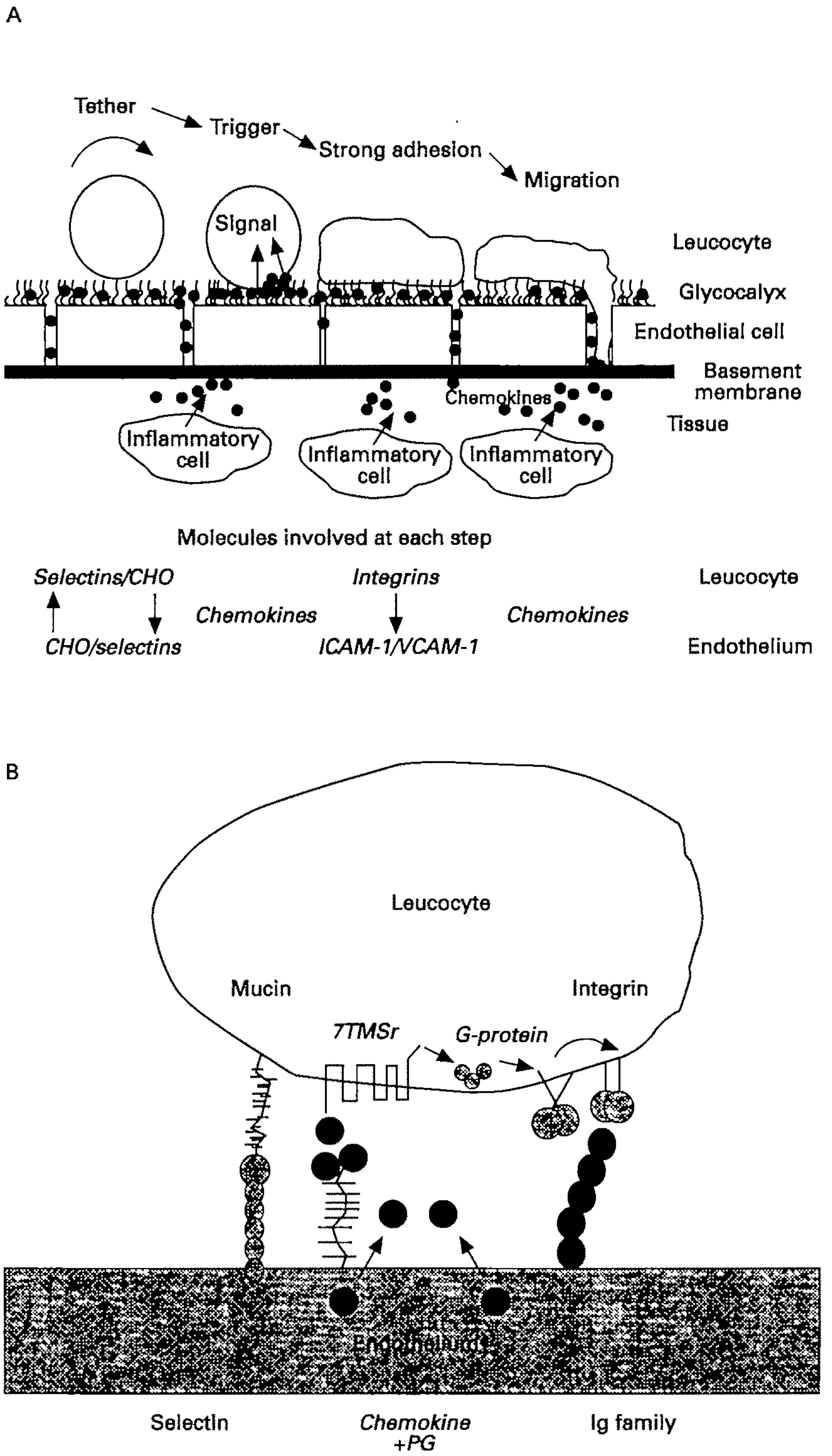

Figure 4 Adhesion to endothelium and subsequent transendothelial migration is regulated by a cascade of interactions between the leucocyte and the endothelium. A: The first step (primary adhesion) involves tethering of the leucocyte to the endothelium by comparatively weak and transient bonds provided by selectins on either the endothelium (e.g. E-selectin) or the leucocyte (L-selectin) that bind to carbohydrate receptors on the opposing cell. This allows the leucocyte to come into contact with pro-adhesive factors (typically chemokines) that are immobilized in the endothelial glycocalyx and provide a trigger for integrin activation and strong secondary adhesion. This strong adhesion is mediated by leucocyte integrins binding to members of the immunoglobulin superfamily on the vessel wall. The final step in the cascade is transendothelial migration which is promoted by chemotactic factors such as chemokines. Chemokines are produced by the endothelium itself or by inflammatory cells in the subendothelial tissues. B: Diagrammatic representation of the major molecules involved in the adhesion cascade between leucocytes and endothelium. The tethering step is provided by selectins and allows chemokines immobilized on proteoglycan in the endothelial glycocalyx to engage specific receptors on the leucocyte. This results in conformational activation of leucocyte integrins permitting their adhesion to endothelial receptors of the immunoglobulin family. In addition, chemokines promote cytoskeletal changes and the induction of motility.

followed later by macrophages and T-cells if the lesion becomes chronic. Such complex inflammatory responses must be mediated by specific mechanisms capable of recruiting particular subsets of leucocytes dependent on the inflammatory stimulus [97].

LEUCOCYTE RECRUITMENT TO TISSUE IS REGULATED BY SEQUENTIAL ADHESIVE INTERACTIONS WITH ENDOTHELIUM

Clearly leucocyte migration must be carefully regulated both to maintain immune surveillance and to enable different inflammatory responses to invading stimuli to be established. For instance, inappropriate recruitment of granulocytes to normal tissue could result in tissue damage from release of proteolytic enzymes and reactive oxygen intermediates whereas a failure of T-cells to migrate through normal tissue would impair immune surveillance. The fact that leucocytes must first recognize and then bind to the endothelium before they can migrate into tissue provides a powerful mechanism for regulating their recruitment. This adhesive interaction with endothelium is a dynamic process involving the activation both of the endothelium and the leucocyte [6, 97]. Leucocyte recruitment occurs when a cascade of sequential interactions between the leucocyte and the endothelium results in the flowing leucocyte coming into contact with the endothelium, stopping at the vessel surface and then migrating into tissue in a regulated manner.

The first step in this process is primary adhesion, or "tethering" which slows the flowing cell by inducing it to roll or bump along the endothelium. After this initial encounter cells may either disengage and be carried away by the flow or, in the presence of the correct triggering factor, undergo secondary adhesion during which binding to the endothelium is stabilized and the leucocyte changes shape, becomes flattened and strongly adherent to the vessel wall. Over the next few minutes the cell migrates between the endothelial cells into tissue, a process termed diapedesis.

Thus, there are four requirements for leucocyte recruitment: (1) tethering or primary adhesion, (2) triggering of strong adhesion, (3) strong adhesion, and (4) transendothelial migration into tissue.

MULTIPLE ADHESION MOLECULES ARE INVOLVED IN LEUCOCYTE BINDING TO ENDOTHELIUM

A number of structurally diverse adhesion molecules, are involved in this adhesion cascade [6, 21] (fig. 4 and table 1). The expression of these molecules is regulated with differentiation and activation both of the endothelium and the leucocyte and is therefore a dynamic process in which both cell types play an active role [97].

Table 1 Some of the molecular pairs involved in leucocyte endothelial adhesion. CHO represents carbohydrate receptors of which there are several. * Expressed on particular subsets of T-lymphocytes. Broken lines represent interactions, the exact role of which has not yet been characterized. HA = hyaluronate, FN = fibronectin, LN = laminin.)

T-cell		Endothelium		Neutrophil
L-selectin	→	CHO	←	L-selectin
CHO*	→	E-selectin	←	CHO
CHO*	→	P-selectin	←	CHO
LFA-1	→	ICAM-1	←	MAC-1
LFA-1	→	ICAM-2		
VLA-4	→	VCAM-1		
CD44	⇢	HA,FN,LN	⇠	CD44
CD31	⇢	?CD31	⇠	CD31

Selectins mediate primary, tethering adhesion

A family of lectin-like adhesion molecules called selectins support leucocyte rolling under flow conditions when they bind to carbohydrate receptors [51]. One of these molecules, L-selectin, is widely expressed on leucocytes. Different leucocytes express distinct forms of L-selectin which can undergo extensive post-translational modification by glycosylation thereby altering receptor specificity. Thus, L-selectin expressed by naive T-cells binds receptors on lymph node endothelium and is involved in the homing of naive cells to lymphoid tissue [73], whereas L-selectin on neutrophils does not mediate binding to lymph node endothelium but instead supports binding to inflamed endothelium.

Two other selectins, E-selectin (CD62E) and P-selectin (CD62P) are synthesized and expressed by endothelial cells after cytokine activation with, for example, IL-1 or TNFα. E-selectin binds to poorly defined oligosaccharide receptors on neutrophils and monocytes and to a subset of CD4+ memory T-cells which express a receptor called the cutaneous lymphocyte antigen [92]. P-selectin is also expressed by activated endothelium and by platelets. P-selectin can be rapidly mobilized from cytoplasmic granules (Weibel-Pallade bodies) to the endothelial cell surface on activation. Although most interest has focused on the ability of P-selectin to mediate neutrophil rolling a subset of T-cells can also bind to P-selectin *in vitro* suggesting a possible role for this molecule in T-cell endothelial interactions [31]. Thus, each selectin recognizes specific carbohydrate sequences and different combinations of receptor and ligand will promote the recruitment of particular leucocyte subsets.

Three properties make selectins ideal mediators of primary adhesion/tethering:

(i) Structure and localization. E-selectin and P-selectin are long molecules that extend out of the surrounding endothelial glycocalyx to make contact with passing leucocytes and L-selectin is concentrated on the tips of leucocyte microvilli where it can best make contact with the endothelial surface.

(ii) Selectins mediate activation-independent adhesion. Leucocytes do not require prior activation to interact with selectins. This is important for an initial adhesive interaction which will take place with a circulating leucocyte that has not yet come into contact with local activating factors.

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(iii) Selectins mediate transient and comparatively weak adhesion. This tethering allows the leucocyte to come into contact with the endothelium but to subsequently disengage if further strong adhesion is not triggered [51].

It has recently been reported that other molecules can mediate primary adhesion of lymphocytes [72]. For example, the integrin ligand VCAM-1 can mediate both primary (tethering) and secondary (strong) adhesion [44]. This may be particularly important in low-flow systems such as the lung, liver and spleen. Furthermore, in these systems it is possible that strong, integrin-mediated adhesion can take place without prior tethering.

Triggering of integrin-mediated adhesion by secreted factors

Strong, secondary adhesion to endothelium is mediated by leucocyte adhesion molecules of the integrin family. A characteristic property of integrins is their requirement for conformational activation before optimal ligand binding can occur [42]. Thus, a triggering step is required in the cascade during which integrins are functionally activated to bind to an appropriate endothelial counter-receptor [6].

Trigger factors for leucocytes fall into two broad categories: (i) cell surface molecules, and (ii) cytokines and secreted factors. The former include L-selectin which, in addition to mediating tethering, can also transmit activating signals to leucocyte integrins when engaged by an appropriate receptor [93] and CD31, an adhesion molecule of the immunoglobulin superfamily that is widely expressed on endothelium and on a restricted subset of T-cells. Engagement of CD31 on these T-cells leads to a conformational change in the T-cell integrins LFA-1 and VLA-4 resulting in activation of binding to the endothelial ligands ICAM-1 and VCAM-1 [102]. Despite the above observations it is likely that the most important adhesion triggers are cytokines and secreted factors.

Pro-adhesive factors for neutrophils and monocytes. It has been known for many years that a diverse group of soluble factors can act as chemoattractants for neutrophils and monocytes (table 2). These include bacterial-derived proteins such as the formyl peptides of which f-met-leu-phe (fMLP) is the best known, C5a, a complement component, leukotriene B4, an eicosanoid, and platelet-activating factor (PAF), a product of phosphatidyl choline metabolism [97]. In addition, neuropeptides such as the endorphins have recently been shown to act as neutrophil chemoattractants [114]. As well as promoting chemotaxis many of these factors also activate leucocyte adhesion. Thus, they may play a dual role both as trigger factors and chemotactic factors, thereby promoting transendothelial migration into tissue.

By their nature one would expect the above factors to be released at sites of bacterial invasion or tissue injury. Consistent with this, their actions are largely restricted to cells of the myelomonocytic lineage which are rapidly recruited during acute inflammation. They do not have strong actions on lymphocytes and cannot, therefore, provide all the necessary signals to explain the specificity of leucocyte subset recruitment. The discovery of the chemokine family of chemotactic cytokines has provided the extra options which allow the paradigm to be extended to other leucocytes, notably lymphocytes [24, 97].

Table 3 Structural chemokine families. The C-C chemokines and the non-ELR subfamily of the C-X-C chemokines act predominantly on monocytes, lymphocytes and eosinophils. The ELR C-X-C chemokines act on neutrophils and lymphotactin acts only on lymphocytes (for more details see text and ref.[15]

C-C Csome 17	C Csome 1	C-X-C Csome 4	
		ELR	
I309	Lymphotactin	ENA-78	
MCP-1	SCM-1	GCP-2	
MCP-2		IL-8	
MCP-3		MGSA	βTG
MIP-1α		PBP	CTAP-III
MIP-1β			NAP-2
RANTES			
		non-ELR	
		IP-10	
		MIG	
		PF-4	

The role of chemokines in leucocyte subset recruitment. Chemokines are a family of structurally distinct cytokines, that are chemotactic and proadhesive for leucocyte subsets [52, 67, 81]. There are over 30

Table 2 Examples of different soluble factors that can trigger leucocyte chemotaxis. The growth factors described here are also cytokines in that they act on and between cells of the immune system; they have been included in a separate category here because, owing to their potent growth regulatory effects on other cell types, they are more commonly perceived as growth regulators rather than as immune regulators. Likewise, the term cytokines refers to the classic cytokines and excludes chemokines which are shown separately

	Neutrophil	Monocyte	Lymphocyte
Chemokines	IL-8	MCP-1	RANTES
Bacterial peptides	FMLP	FMLP	?
Complement	C5a	C5a	—
Eicosanoids	LTB-4	LTB-4	?LTB-4
Phospholipids	PAF	PAF	?
Growth factors	TGFβ	TGFβ	HGF
Cytokines	—	—	IL-2
Opioids	L-enkephalin	L-enkephalin	β-endorphin

Table 4 Different chemokines preferentially act on different subsets of leucocytes. Most of the C-X-C chemokines act on neutrophils whereas the actions of C-C chemokines tend to be directed at mononuclear cells (for more details see ref. [97])

	L	NK	Mono	BAS/EOS	PMNs
IP-10	+++	++	?	–	–
IL-8	++	–	–	–	+++
MGSA/gro	–	–	–	–	+++
ENA-78	–	–	–	–	+++
NAP-2	–	–	–	–	+++
RANTES	+++	+	+++	+++	–
MIP-1α	+++	++	++	++	–
MIP-1β	+++	+	+	++	–
MCP-1	+++	+	+++	++	–
MCP-2	++	+	+++	?	–
MCP-3	+	+	+++	+++	++
Lymphotactin	+++	++	–	?	–

known human chemokines all of which have a characteristic structure and share sequence homology [15]. They can be divided into three subfamilies based on their structure (see table 3). α- and β-chemokines have two disulphide bonds between a total of four cysteine residues whereas the C chemokines have only two cysteines. The α-chemokines, also known as C-X-C chemokines, are distinguished from β-chemokines or C-C chemokines because the first two cysteine residues from the N-terminal are separated by an intervening amino acid (hence C-X-C) whereas in the β-chemokines they are adjacent (C-C). These structural distinctions are important since they confer on chemokines the ability to act on particular leucocyte subsets (table 4). Thus, most of the C-X-C chemokines which include IL-8 and gro/MGSA act predominantly on neutrophils whereas the C-C chemokines (RANTES, MCP-1) act on lymphocytes, monocytes and eosinophils; lymphotactin, the only C-family chemokine that has been functionally characterized so far acts solely on lymphocytes [48].

Some chemokines, i.e. IL-8 and MCP-1, are widely expressed in cells including platelets, leucocytes, endothelium and epithelium, whereas others have a more restricted distribution. Chemokines are expressed a low concentrations in resting cells but are rapidly upregulated on activation when chemokine mRNA can comprise up to 1 % of total cellular mRNA. The factors that activate cells to secrete chemokines vary depending on cell type, site and chemokine and include pro-inflammatory cytokines such as IL-1, TNFα, gIFN, the bacterial cell wall product lipopolysaccharide and chemical mitogens such as phorbol esters.

All of the chemokines so far isolated bind to a family of G-protein-linked, transmembrane spanning receptors [61]. This family also includes the receptors for fMLP, C5a and LTB4. There are many chemokine receptors with differing ligand specificities.

They can be broadly and conveniently categorized into:

(i) specific receptors that only bind a particular chemokine: for example the IL-8RA receptor only binds IL-8;

(ii) receptors with restricted specificity such as the C-C chemokine receptor CKR-1 which binds most of the C-C chemokines but does not bind C-X-C chemokines and the IL-8 receptor RB which binds C-X-C but not C-C chemokines;

(iii) promiscuous receptors such as the Duffy blood group antigen which is expressed on red blood cells and endothelium and binds all known chemokines.

Engagement of leucocyte chemokine receptors by ligand results in calcium mobilization, phosphokinase C (PKC) activation and cytoskeletal rearrangement within the cell. The functional consequences of this include enhanced migration and conformational activation of cell surface integrins to facilitate binding to ligand. Thus, IL-8 activates β2 integrin-dependent adhesion of neutrophils whereas macrophage inflammatory protein-1β (MIP-1β), the first cytokine reported to trigger T-cell adhesion, activates the T-cell β1 integrin VLA-4 to bind to its endothelial counter-receptor VCAM-1 [100]. Since then several other chemokines have been shown to have such an effect; these include MIP-1α, macrophage chemotactic protein-1 (MCP-1), RANTES and interferon-inducible protein-10 (IP-10) [103].

Why can so many diverse cytokines trigger leucocyte adhesion to endothelium? There are two possible explanations: first, that this function is so crucial to host survival that several mechanisms have evolved resulting in a degree of redundancy. This possibility is being investigated in animal models using antibodies to neutralize particular chemokines and then testing the ability of the animal to respond to an inflammatory stimulus. Recently, mice have been developed in which the gene for a particular chemokine has been deleted. Such knock-out mice will provide valuable insights into the role of individual chemokines. The second possibility is that specificity within the chemokine family is tightly regulated and requires the existence of multiple chemokines to provide the required options. There is some evidence for this and it seems likely that specificity acts at several levels, for instance:

(i) Specificity for leucocyte subsets. If particular chemokines act on specific subsets of leucocytes multiple chemokines will be required to account for

Table 5 Combinations of molecular interactions mediate leucocyte subset recruitment. Each leucocyte can select one of several options at each step in the adhesion cascade. The individual interactions will not necessarily confer selectivity on recruitment but the combination of sequential interactions does. Examples are given for combinations that will result in the selection of distinct leucocyte subsets (for more details see ref. [97])

	Neutrophil	Monocyte	Naive T-cell	Skin memory T-cell
Primary adhesion	SLeX–E-selectin	PSGL1–P-selectin	L-selectin–CD34	CLA–E-selectin
Trigger	IL-8	MCP-3	MIP-1β	MCP-1
Secondary adhesion	Mac1–ICAM-1	Mac1–ICAM-1	LFA1–ICAM-2	VLA4–VCAM-1
Migration	PAF	MCP-3	MIP-1β	MCP-1

the selectivity of leucocyte recruitment. For example, gro acts on neutrophils but not on eosinophils or lymphocytes whereas RANTES acts on eosinophils and lymphocytes but not neutrophils [48, 82, 83]. Furthermore, there is evidence for preferential activity within T-cell subsets, for instance MIP-1β affects naive T-cells whereas RANTES and MCP-1 affect memory T-cells [4, 100].

(ii) Restricted tissue expression of chemokines. Distinct chemokines are required to recruit cells to particular sites. For example, IL-8 and MCP-1 are expressed by epithelial cells and may have a particular role in recruiting cells to combat invading pathogens at epithelial surfaces.

(iii) Differences are response to activating stimuli. Different chemokines are induced by particular pro-inflammatory cytokines. For example, the secretion of C-C chemokines such as MCP-1 is enhanced by γIFN whereas the secretion of most C-X-C chemokines such as IL-8 is inhibited.

There is evidence that all of these factors are important. However, there is overlap in the actions of most of the chemokines and the specificity of leucocyte recruitment is almost certainly regulated by the combined effects of all the elements in the adhesion cascade rather than by a highly specific chemokine (table 5).

Pro-adhesive factors act as immobilized ligands. In order to trigger adhesion and transendothelial migration effectively, pro-adhesive factors must be available at the vessel wall where they can interact with circulating leucocytes. Immunohistochemical studies have demonstrated chemokine staining on the vessel lumen and the mechanism of their retention in the endothelium has recently been elucidated (fig. 4). Chemokines have glycosaminoglycan binding motifs that allow them to bind proteoglycans in the endothelial glycocalyx and thereby be retained at relevant sites [79, 100, 101]. An extra layer of complexity is provided by recent reports showing differences in the affinity of chemokines for particular proteoglycans. Since endothelial proteoglycans vary between different sites and can be altered in inflammation; this may add to the selectivity of site-specific recruitment [111].

The chemokines that are retained in the endothelial glycocalyx may come from two distinct sources. First, the endothelium itself has the capacity to secrete a range of chemokines on activation, including IL-8 and MCP-1. Alternatively, inflammatory cells, such as monocytes and fibroblasts beneath the endothelium, secrete chemokines that are subsequently transported to and retained in the endothelial glycocalyx.

Another pro-adhesive factor, PAF, is also present at the vessel wall although the mechanism of its retention there is different. PAF is a phospholipid which is produced by endothelial cells within minutes of activation by thrombin, histamine or leukotriene. It is expressed at the endothelial surface but not released into the fluid phase. This endothelial-associated PAF can trigger neutrophil β2-integrin activation and promote transendothelial migration.

Strong, secondary adhesion is mediated by leucocyte integrins that bind members of the immunoglobulin superfamily on endothelium

Integrins are a family of heterodimeric membrane glycoproteins that can be grouped into families based on their β subunit [7, 96]. The most important integrins for leucocytes are the β1- and β2-integrins. The β1-integrins include VLA-4 which is expressed on lymphocytes and monocytes, but not neutrophils. VLA-4 consists of a common β-chain (CD29) paired with the α-chain CD49d. It binds to the endothelial receptor VCAM-1 (CD102). VCAM-1 is absent from most non-inflamed endothelium but is expressed in response to pro-inflammatory cytokines and IL-4. The β2-integrins consist of LFA-1 (β-chain CD18 paired with α-chain CD11a), MAC-1 (CD11b/Cd18) and gp150,95 (CD11c/CD18). LFA-1 is the dominant β2-integrin on lymphocytes but is also expressed on other leucocytes. It binds to two members of the intercellular adhesion molecule (ICAM) family of adhesion molecules, that are expressed on endothelium; ICAM-2 (CD) is constitutively expressed and mediates binding to resting endothelium, whereas ICAM-1 (CD54) expression is increased with activation and predominates in binding to inflamed endothelium [97]. MAC-1 (CD11b/CD18) is the dominant integrin on neutrophils and monocytes. It binds to ICAM-1 on activated endothelium. GP150,95 does not bind directly to endothelium although it can interact with endothelium via its ability to bind fibrinogen [71].

The expression of integrin ligands by activated endothelium at sites of inflammation *in vivo* depends upon the nature of the endothelial-activating stimulus. For instance, both ICAM-1 and VCAM-1 can be induced on resting endothelium by exposure to the pro-inflammatory cytokines tumour necrosis factor α (TNFα), IL-1 and gamma interferon (γIFN) whereas IL-4 selectively induces VCAM-1 expression [84, 91]. Furthermore, there are differences in the adhesion molecules expressed by endothelial cells from different tissues and in their responses to pro-inflammatory cytokines.

Migration

After binding strongly to endothelium the leucocyte migrates between the endothelial cells into tissue in a process called transendothelial migration or diapedesis. As mentioned above, many of the cytokines that trigger strong adhesion can also act as chemotactic factors to promote transendothelial migration [4, 100, 103]. Thus IL-8 induces chemotaxis of neutrophils as well as triggering their adhesion and MIP-1β can induce both adhesion and migration of T-lymphocyte subsets. As discussed below migration is dependent on regulated adhesion and de-adhesion as well as on cytoskeletal rearrangement within the cell and it is not therefore surprising that these properties are frequently shared.

COMBINED EFFECTS OF SEQUENTIAL INTERACTIONS DETERMINE LEUCOCYTE SUBSET RECRUITMENT

The adhesion cascade provides a powerful model for controlling the specificity of leucocyte subset adhesion to endothelium that can be both rapidly amplified and carefully controlled. Specificity and regulation can be introduced at each of the sequential interactions giving rise to the paradigm proposed by Butcher and Springer of "area codes" for leucocytes [24, 97]. Thus, a particular leucocyte will have several options at each step of the cascade and it is the combined effects of the interactions that will determine the specificity of recruitment.

Regulation of leucocyte adhesion—physiological control *vs* pathological disorder

MULTI-STEP ADHESION IS A CONTROL STRATEGY THAT MAY BE SUBVERTED

Circulatory and molecular considerations outlined above suggest that selectin-mediated rolling adhesion is a prerequisite for leucocyte immobilization because it allows pick-up of localized signal(s) and because, for neutrophils at least, immobilizing integrin-mediated attachment cannot operate rapidly enough to capture flowing cells. However, multi-step adhesion is not an absolute necessity in the sense that lymphocytes can be immobilized by a single integrin–immunoglobulin interaction [11] and that parasitized red cells can be immobilized by endothelial receptors directly from flow [29]. This suggests that rolling is part of an evolved control strategy rather than a physical necessity, and that signalling is the limiting process in multi-step adhesion. With rolling itself dependent on an endothelial response to stimulus, and neutrophil stabilization dependent on pick-up of signal from the endothelium after initial attachment, several controllable responses must occur in order to complete immobilization.

Even then, further regulated steps must underlie onward neutrophil locomotion (which requires continual modulation of adhesive interaction to allow detachment at the rear of the cell and new attachment at the front), and migration in a preferred direction. The concept that neutrophils can move along a concentration gradient of chemoattractant is well established [27], and one can foresee the existence of such a gradient in connective tissue containing an inflammatory stimulus. However, it is not clear how a gradient could be established in the presence of flowing blood, and so it seems that the neutrophils move across the surface and between endothelial cells along some other guideline. Taken together, migration requires a sequence of events and transformations, open to control at each stage and dependent on incompletely understood signalling responses. It is not surprising that multiple regulatory steps exist because, for instance, if neutrophil adhesion and migration were to proceed without tight control, then the potential for amplification of a catastrophic inflammatory reaction would be great. This raises the question as to whether pathological events follow a similar pattern and rely on the "normal" control sequence or whether various of the regulated steps are missing or out of order, bringing about uncontrolled and potentially damaging leucocyte–endothelial interaction.

KINETICS OF TRANSFORMATIONS IN THE MULTI-STEP SEQUENCE MAY BE CRITICAL FACTORS IN ITS OUTCOME

If the multi-step process represents a strategy for controlling adhesion and migration, then the rate at which transformation between steps occurs will have a critical influence on the outcome. As noted above, capture of flowing blood cells requires a fast-acting adhesive interaction, but the kinetics of transformation to stable attachment may also be important. Several studies now show that initial tethering events may be short-lived and leucocytes may only make brief initial contact with endothelium, especially if receptors such as selectins are expressed at low level [10, 16]. This may be an advantage, in that if signals are not present, the tethered leucocytes will be swept away. It does imply, however, that signalling and leucocyte responses must be rapid for immobilization to be achieved. Indeed, recent studies show that short-lived interactions can underlie successful, signal-dependent immobilization of lymphocytes in lymph nodes [16], and our own observations indicate that neutrophils can respond to adhesion-promoting, activating stimuli in seconds and probably even more rapidly [76, 90]. When rolling adhesion is more long-lived, there may not appear to be a necessity for such rapid signalling, but if leucocytes are to be localized accurately, then they must still come to a halt within a short distance of exposure to stimulus.

Clearly this can only be achieved by localizing the stimulus, i.e. as noted above, on the cell surface rather than relying on the fluid phase. Moreover, failure to localize the stimulus or the cell response would lead to undesirable dispersal of active cells or mediators into the systemic circulation.

After immobilization of leucocytes on the endothelial surface, transformation to migration might be able to occur at a more leisurely pace. However, its successful completion is necessary because otherwise the vessel lumen is in danger of occlusion, and because the immobilized neutrophil contains an arsenal of lytic enzymes, has great oxidant potential and is capable of producing mediators which could attract further leucocytes to the site. In fact, it is unclear how activated neutrophils order such events. *In vitro* stimuli tend to induce oxidative bursts, degranulation and release of mediators along with pro-adhesive changes. *In vivo*, adhesion must come first, followed by migration, and then the destructive potential needs to be unleashed on contact with foreign bodies or necrotic tissue. Thus, there must be a lag of the order of minutes and a dissociation of the responses that is not always evident *in vitro*. We have seen very high levels of neutrophil attachment and migration on cytokine-stimulated endothelial cells without apparent damage to the monolayer (unpublished observations), so that some form of "pathological" priming such as hypoxia may be required to induce neutrophils to cause endothelial damage [43]. Control and localization of the neutrophil lytic response might come about through some endothelial regulatory factor (such as nitric oxide) and it may be that stimulation protocols used for neutrophils in suspension *in vitro* do not mimic the situation when initial stimuli are presented on the endothelial surface.

Adhesive leucocytes must thus clear the vessel lumen before proceeding to other functional responses. Otherwise obstruction in the lumen could be amplified by neutrophil–neutrophil interaction, such as homotypic aggregation and transfer of activating agents such as PAF and Il-8. At high levels of neutrophil adhesion in *in vitro* flow models we have found evidence of activated adherent cells forming contacts and building quite large aggregates if they cannot transmigrate [G. E. Rainger, G. B. Nash, unpublished observations]. Thus, uncontrolled adhesion could lead to impaired perfusion and intravascular damage if neutrophils do not migrate, as well as destruction of surrounding tissue if they do.

DO PATHOLOGICAL EVENTS FOLLOW THE PHYSIOLOGICAL SEQUENCE?

The foregoing suggests two main possibilities: that pathological adhesive interactions follow a normal controlled sequence, but that they occur at an inappropriate or undesired time or over a prolonged period; that disordered or unregulated processes lead to uncontrolled build up of leucocytes and tissue damage, for example if activation occurs before immobilization or cells fail to complete the full response. In fact, both scenarios are likely *in vivo*. Although rolling, signalling, stopping and migration may occur in sequence (perhaps after hypoxia and reoxygenation judging from *in vitro* studies [75]), steps might be missed out under special circumstances. The necessity for selectin-mediated adhesion might be lost, for example, under low-flow conditions where activated integrins would be able to immobilize neutrophils directly [70], or in tissues with unusual architecture or flow pattern, such as the lungs. Moreover, the initial step might be mechanical rather than adhesive. Impaired neutrophil deformability is associated with number of ischaemic disorders [62, 64, 65], smoking [89] and circulating antineutrophil cytoplasm antibodies associated with autoimmune vasculitis [25]. Loss of deformability has been shown to be capable of causing trapping of neutrophils in the lungs independent of adhesion [112], and so adhesive and damaging interactions could follow on from mechanical changes without initial endothelial exposure of tethering molecules. Moreover, it may not be correct to treat mechanical and adhesive responses as separate, because the time courses of each are similar (rapid initial phase in seconds, followed by modulation over minutes), and there is evidence that skeletal structures within the cell regulate adhesive behaviour [46].

The concept of out-of-order adhesion is not so well documented, although it is known that if eosinophil integrins are "frozen" in an activated state the cells can no longer migrate [50]. Successful neutrophil immobilization seems to rely on activation of constitutive integrins while migration requires integrin deactivation and successive waves of new integrin expression and activation [41, 90]. Disruption of this sequence might interfere with its continuation. Activated neutrophils bind to resting endothelial cells but show little migration compared with neutrophils bound to cytokine-treated endothelium (unpublished observations), so that activation of only one side of the leucocyte–endothelial interaction results in an incomplete response. As noted above, the phagocytic and lytic responses of leucocytes need to occur at the right time, and there is the hypothetical possibility at least that pathology can arise if they are induced before migration. Compared with the current quite extensive knowledge of adhesion molecules themselves, the regulation of transformations (rolling to stopping; stopping to migration; migration to phagocytosis/degranulation) is an outstanding puzzle, and its manipulation may be a route to achieving control of inflammation.

DO OTHER CELL–CELL INTERACTIONS INCREASE THE PATHOLOGICAL POTENTIAL OF ADHESION BETWEEN LEUCOCYTES AND ENDOTHELIUM?

Adhesion of leucocytes to endothelium may be the primary promoter of vascular pathology, but there are other forms of intercellular interaction with "physiological" or "pathological" potential that are worthy of comment (fig. 5). As noted previously, monocyte/macrophages provide cytokines and chemokines which can activate endothelium, neutrophils and lymphocytes. Less well recognized is the

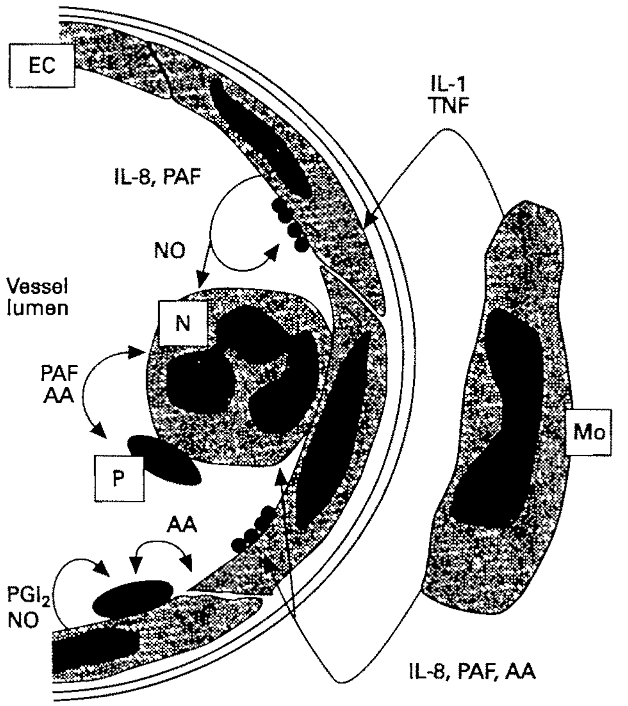

Figure 5 Cell–cell interactions that may potentiate or regulate adhesion of neutrophils (N) to vascular endothelial cells (EC). Endothelial cells manufacture and present the activating signals IL-8 and platelet-activating factor (PAF), and the regulatory factor nitric oxide. Arachidonic acid and its metabolites may be exchanged between neutrophils, endothelial cells, platelets (P) and monocytes (Mo). Monocytes manufacture IL-8 and PAF, as well as cytokines (TNF and IL-1) which activate endothelial expression of adhesion molecules. Platelets can present an additional adhesive surface for neutrophils, a process probably inhibited by nitric oxide (NO) and prostacyclin (PGI_2) from endothelial cells. Activated components of complement (e.g. C5a) may be derived from surrounding tissue, e.g. after hypoxia.

likelihood that platelets modulate the inflammatory response. Platelet attachment to sub-endothelial matrix is an essential part of haemostasis. However, they can also bind to leucocytes in blood and can act as an adhesive surface for flowing leucocytes [26, 78], interactions of uncertain physiological function. Immobilized platelets support both rolling attachment of unstimulated neutrophils and stationary attachment of activated cells [26, 90]. In addition, platelets and neutrophils are capable of releasing factors which activate each other and the response of each to stimulus is greater in the presence of the other, for example because of their capability to exchange metabolites of arachidonic acid (eicosanoids) and because of release of neutrophil granule enzymes (see ref. [63] for review). Thus, one may predict that co-localization of platelets and neutrophils would amplify the inflammatory response, and evidence from animal models suggest that reperfusion injury and thrombosis in vessel grafts are indeed augmented by their interaction [58, 68]. It may also be worth noting that biochemical interactions may be three-cornered, including the endothelial cells which release factors modulating platelet response (e.g. prostacyclin and nitric oxide) but can also participate in exchange of metabolites of arachidonic acid with platelets and neutrophils [56].

Interaction between leucocytes may also occur within the lumen. Homotypic aggregation between neutrophils occurs after stimulation in purified suspensions and in blood, and is associated with agents such as activated components of complement (e.g. generated during haemodialysis) [30, 49]. The mechanism of aggregation appears to involve both integrin- and selectin-mediated adhesion [94]. If an immobilized neutrophil acts as a focus for attachment of others flowing past, then the potential for vascular occlusion is great; alternatively, aggregates formed in the blood would block small vessels directly. The circulatory conditions under which such interactions occur and the molecular mechanisms appear worthy of further attention.

Leucocyte–endothelial interactions and disease

Leucocyte–endothelial interactions are vital for effective host defence against pathogens and when they fail overwhelming sepsis can result. This is best illustrated by two rare inherited disorders—leucocyte adhesion deficiency type 1 (LAD-1) and type 2 (LAD-2) that are associated with deficiency of CD18 and sialyl Lewis X respectively. Both syndromes result in dramatically reduced neutrophil recruitment to sites of inflammation and are associated with recurrent life-threatening sepsis.

In addition to their role in protecting the host, leucocyte–endothelial interactions can contribute to the generation of unwanted, pathological inflammation in such conditions as reperfusion injury after ischaemia, septic shock, autoimmunity, allergic responses and allograft rejection. For example, pulmonary infiltration as part of the adult respiratory distress syndrome (ARDS) is a serious complication of septic shock resulting from acute pancreatitis. Although the original focus of disease is distant from the lung, neutrophils are inappropriately recruited to the pulmonary bed because of enhanced adhesion to the pulmonary microvasculature. The increased adhesion of leucocytes to microvasculature in the liver, lung and kidney is a crucial factor in the development of MOF in septic shock and, as discussed above, results from increased rigidity and inappropriate activation of adhesion molecules on circulating leucocytes [37] or from activation of the endothelium by circulating factors such as endotoxin or LPS [23]. The role of leucocyte adhesion to endothelium in this setting is demonstrated by the fact that the development of ARDS can be inhibited by the administration of antibodies to block CD18 or the use of oligosaccharides that block leucocyte binding to selectins [59]. In addition, mice that are genetically deficient in ICAM-1 are resistant to the fatal complications of septic shock [22].

Increased expression of endothelial adhesion molecules is associated with a range of inflammatory disorders from graft rejection to liver cirrhosis [21]. Acute inflammatory disorders are associated with infiltration by neutrophils and tend to be accompanied by increased expression of E-selectin and P-selectin whereas in chronic, lymphocytic inflammation ICAM-1 and VCAM-1 expression predominate. Thus, E-selectin is strongly expressed on endothelium in acute appendicitis and is found in high concentrations in the circulation in septic shock, whereas VCAM-1 is induced during the chronic inflammation of sarcoidosis and graft rejection, conditions associated with a lymphocytic infiltrate [66]. However, these distinctions are often less clear-cut and E-selectin, ICAM-1 and VCAM-1 may be expressed together at sites of chronic inflammation. However, caution should be used when interpreting studies based on increased expression of adhesion molecules [74]. The presence of a particular adhesion molecule does not always imply it has a functional role in that particular clinical setting. For example, E-selectin is upregulated on endothelium in the chronic immune-mediated liver disease, primary biliary cirrhosis, suggesting it is important for the generation of the chronic inflammatory infiltrate. However, very few of the infiltrating leucocytes in this disease express receptors capable of binding E-selectin suggesting that E-selectin expression in this disease is a consequence of the local inflammation and of no direct relevance to leucocyte recruitment [8].

There are now accumulating data on chemokine expression in a number of inflammatory diseases. Transplant graft rejection is associated with increased tissue expression of RANTES, ENA-78, MIP-1α and MIP-1β [2, 69, 86] and a wide range of other immune-mediated diseases have been associated with increased chemokine expression and secretion [19, 40, 77, 87, 95]. The ability of IL-8 to trigger neutrophil recruitment suggests it will be involved in the inflammatory response of sepsis and several studies have shown increased circulating IL-8 in patients with septic shock [57]. In addition, anti-IL-8 treatment can ameliorate some of the features of sepsis in animal models. It has recently been suggested that MIP-1α also plays a crucial role in septic shock and it is likely that a network of chemokines will be involved in this complex disease [55, 98].

Thus, in order to understand the pathogenesis of an inflammatory response one requires a detailed understanding of the dynamic regulation of all elements in the adhesion cascade.

SOLUBLE ADHESION MOLECULES IN INFLAMMATION

Many cell surface adhesion molecules are shed into the fluid phase in response to cellular activation [66, 80]. These include the leucocyte adhesion molecules L-selectin and CD31 and the endothelial adhesion molecules ICAM-1, VCAM-1 and the selectins. The functions of soluble adhesion molecule release are not known. There is evidence that soluble E-selectin can activate neutrophils suggesting it might act as an inflammatory mediator [53]. Alternatively other groups have suggested that soluble adhesion molecules are a homeostatic mechanism to block adhesion and downregulate inflammatory responses [35]. Whatever their functional significance soluble CAMs are markers of inflammation in a range of acute and chronic inflammatory disorders [3, 5, 35]. However, few studies have shown any great prognostic or diagnostic advantage in measuring adhesion molecules compared with other markers of inflammation.

THERAPEUTIC IMPLICATIONS

The recent advances made in understanding the molecular basis of leucocyte–endothelial interactions suggest new approaches for therapeutic intervention in a range of inflammatory diseases [1]. Monoclonal antibodies that block the function of particular adhesion molecules have been used to prevent tissue infiltration by leucocytes in animal models. For example, antibodies to E-selectin prevent antigen-induced airway hyper-responsiveness in a primate model of asthma by inhibiting neutrophil infiltration and in models of reperfusion injury antibodies to ICAM-1 and CD18 have successfully reduced tissue infiltration and damage caused by neutrophils [18, 36, 47, 110]. In addition to therapy aimed at blocking acute inflammation other studies have addressed the treatment of chronic immune disorders. Antibodies to VLA-4 reduce T-cell infiltration into the brain and slow disease progression in a rat model of multiple sclerosis suggesting that anti-adhesion molecule therapy might prove beneficial in autoimmune diseases [17, 113].

Clinical trials of anti-adhesion molecule therapy are few; antibodies to ICAM-1 have shown only limited promise in the treatment of graft rejection and rheumatoid arthritis and the use of murine monoclonal antibodies to treat chronic autoimmune diseases is complicated by the development of neutralizing anti-murine antibodies [32, 39]. The development of humanized or chimeric antibodies overcomes the latter problem but other treatments based on molecular analogues have many pharmacological advantages. Such therapy has recently been tested in animals. Peptides that bind to and block the function of the leucocyte integrin Mac-1 (CD11b) have been used to reduce neutrophil infiltration and tissue damage in bacterial meningitis [105]. Infusions of oligosaccharides containing sialyl-Lewis X, the carbohydrate ligand for P-selectin and E-selectin, prevented neutrophil-mediated lung injury induced by injections of cobra venom, a model with many features that are similar to ARDS [60].

More recently, therapy aimed at blocking chemokines has been tested in animal models of inflammation. Anti-MCP-1 treatment prevents the development of granulomatous lung disease in a murine model [54] and anti-IL-8 treatment reduces reperfusion lung injury [88].

It is likely that the next few years will see the development of new therapies to prevent leucocyte–endothelial interactions by directly inhibiting the adhesion molecules involved or by modulating their regulation by inhibiting cytokine-induced signalling in endothelium or blocking the actions of the chemokines that trigger leucocyte adhesion molecules. However, the complexity of the processes involved suggests that simple approaches to therapy are unlikely to be successful and that blocking a particular molecule may have consequences that were initially unforeseen. It is thus essential that such studies are investigated and set up in the context of the adhesion cascade and tested thoroughly before being applied to clinical disorders such as septic shock.

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References

1. Adams DH. Cell adhesion molecules: targets for therapeutic intervention in liver transplantation. *Journal of Hepatology* 1995; **23**: 225–231.
2. Adams DH, Hubscher SG, Fear J, Johnston J, Shaw S, Afford S. Expression of MIP-1α and MIP-1β after liver transplantation. *Transplantation* 1996; **61**: 817–825.
3. Adams DH, Burra P, Hubscher SG, Elias E, Newman W. Endothelial activation and circulating vascular adhesion molecules in alcoholic liver disease. *Hepatology* 1994; **19**: 588–594.
4. Adams DH, Harvath L, Bottaro DP, Interrante R, Catalano G, Tanaka Y, Strain A, Hubscher SG, Shaw S. Hepatocyte growth factor and macrophage inflammatory protein-1β: structurally distinct cytokines that induce rapid cytoskeletal changes and subset-preferential migration in T cell. *Proceedings of the National Academy of Sciences, USA* 1994; **91**: 7144–7148.
5. Adams DH, Mainolfi E, Elias E, Neuberger JM, Rothlein R. Detection of circulating intercellular adhesion molecule-1 after liver transplantation—evidence of local release within the liver during graft rejection. *Transplantation* 1993; **55**: 83–87.
6. Adams DH, Shaw S. Leucocyte endothelial interactions and regulation of leucocyte migration, *Lancet* 1994; **343**: 831–836.
7. Adams DH, Shaw S, Van Seventer G. Adhesion molecules: role in cellular adhesion and communication. In: Snow EC, ed. *Handbook of T and B Lymphocytes*. San Diego: Academic Press, 1993, 3–25.
8. Adams DH, Williams A, Hubscher SG, Robinson M. Expression of E-selectin (CD62E) and E-selectin ligands in human liver inflammation. *Hepatology* 1996; (in press).
9. Ager A. Lymphocyte recirculation and homing: roles of adhesion molecules and chemoattractants. *Trends in Cell Biology* 1994; **4**: 326–333.
10. Alon R, Hammer DA, Springer TA. Lifetime of the P-selectin-carbohydrate bond and its response to tensile force in hydrodynamic flow. *Nature* 1995; **374**: 539–542.
11. Alon R, Kassner PD, Carr MW, Finger EB, Hemler ME, Springer TA. The integrin VLA-4 supports tethering and rolling in flow on VCAM-1. *Journal of Cell Biology* 1995; **128**: 1243–1253.
12. Athens JB, Haab OP, Raab SO, Mauer AM, Ashenbrucker H, Cartwright GE, Wintrobe MM. Leukokinetic studies. IV. The total blood, circulating and marginal granulocyte pools and the granulocyte turnover rate. *Journal of Clinical Investigation* 1961; **40**: 989–995.
13. Bagge U. Leukocytes and capillary perfusion in shock. In: Meiselman HJ, Lichtman MA, Lacelle PL, eds. *White Cell Mechanics*. New York: Alan R Liss, 1984, 285–294.
14. Bagge U, Branemark P-I. White blood cell rheology. An intravital study in man. *Advances in Microcirculation* 1977; **7**: 1–17.
15. Baggiolini M, Loetscher P, Moser B. Interleukin-8 and the chemokine family. *International Journal of Immunopharmacology* 1995; **17**: 103–108.
16. Bargatze RF, Butcher EC. Rapid G protein-regulated activation event involved in lymphocyte binding to high endothelial venules. *Journal of Experimental Medicine* 1993; **178**: 367–372.
17. Baron JL, Madri JA, Ruddle NH, Hashim G, Janeway CA. Surface expression of alpha4 integrin by CD4 T cells is required for their entry into brain parenchyma. *Journal of Experimental Medicine* 1993; **177**: 57–68.
18. Bautista AP, Spolarics Z, Jaeschke H, Smith CW, Spitzer JJ. Monoclonal antibody against the Cd18 adhesion molecule stimulates glucose uptake by the liver and hepatic non-parenchymal cells. *Hepatology* 1993; **17**: 924–931.
19. Becker S, Quay J, Koren HS, Haskill JS. Constitutive and stimulated mcp-1, gro-alpha, gro-beta and gro-gamma X expression in human airway epithelium and bronchoalveolar macrophages X. *American Journal of Physiology* 1994; **266**: L278–L286.
20. Beverley PCL. Human T-cell memory. *Current Topics in Microbiological Immunology* 1990; **159**: 111–122.
21. Bevilacqua MP. Endothelial–leukocyte adhesion molecules. *Annual Review of Immunology* 1993; **11**: 767–784.
22. Bonavida B, Bradley TP, Grimm EA. The single-cell assay in cell-mediated cytotoxicity. *Immunology Today* 1983; **4**: 196–200.
23. Bonavida B, Fan J, Hiserodt JC. T-cell membrane antigens associated with cytotoxic function. *Immunology Today* 1982; **2**: 138–140.
24. Butcher EC. Leukocyte-endothelial cell recognition: three (or more) steps to specificity and diversity. *Cell* 1991; **67**: 1033–1036.
25. Buttrum SM, Drost EM, Macnee W, Goffin E, Lockwood CM, Hatton R, Nash GB. Rheological response of neutrophils to different types of stimulation. *Journal of Applied Physiology* 1994; **77**: 1801–1810.
26. Buttrum SM, Hatton R, Nash GB. Selectin-mediated rolling of neutrophils on immobilized platelets. *Blood* 1993; **4**: 1165–1174.
27. Cassimeris L, Zigmond SH. Chemoattractant stimulation of leukocyte locomotion. *Seminars in Cell Biology* 1990; **1**: 125–134.
28. Chien S, Schmalzer EA, Lee MML, Impelluso T, Skalak R. Role of white blood-cells in filtration of blood-cell suspensions. *Biorheology* 1983; **20**: 11–27.
29. Cook BM, Berendt AR, Craig AG, Newbold CI, Nash GB. Rolling and static cytoadhesion of red blood cells parasitised by *Plasmodium falciparum*: separate roles for ICAM-1, CD36 and thrombospondin. *British Journal of Haematology* 1994; **87**: 162–170.
30. Craddock PR, Hammerschmidt DE, White JG, Dalmasso AP, Jacob HS. Complement C5a-induced granulocyte aggregation in vitro: a possible mechanism for leukopenia and leukostasis. *Journal of Clinical Investigation* 1977; **60**: 260–264.
31. Damle NK, Klussman K, Dietsch MT, Mohagheghpour N, Aruffo A. GMP-140 (P-selectin/CD62) binds to chronically stimulated but not resting CD4+ T lymphocytes and regulates their production of proinflammatory cytokines. *European Journal of Immunology* 1992; **22**: 1789–1793.
32. Davies MH, Tregunno GA, Scharschmidt L, Neuberger J. Monoclonal anti-ICAM-1 antibodies in liver transplantation—preliminary results of a phase I trial. *Hepatology* 1993; **18**: 75a.
33. Engler RL, Schmidschonbein GW, Pavelec RS. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. *American Journal of Pathology* 1983; **111**: 98–111.
34. Frank RS. Time-dependent alterations in the deformability of human neutrophils in response to chemotactic activation. *Blood* 1990; **76**: 2606–2612.
35. Gearing AJH, Newman W. Circulating adhesion molecules in disease. *Immunology Today* 1993; 14(10): 506–512.
36. Gundel RH, Wegner C, Torcellini CA, Clarke CC, Haynes N, Rothlein R, Smith CW, Letts LG. ELAM-1 mediates antigen-induced acute airway inflammation and late-phase airway obstruction in monkeys. *Journal of Clinical Investigation* 1991; **88**: 1407–1411.
37. Hackett CJ, Sullivan K, Lin YL. Ultrastructure of an influenza virus-specific cytotoxic T cell clone and its interaction with P815 and macrophage targets. *Cellular Immunology* 1982; **68**: 276–286.
38. Harris AG, Skalak TC. Effects of leukocyte activation on capillary hemodynamics in skeletal-muscle. *American Journal of Physiology* 1993; **264**: H909–H916.

39. Haug CE, Colvin RB, Delmonico FL, Auchincloss H, Tolkoff-Rubin N, Preffer FI, Rothlein R, Norris S, Scharschmidt L, Cosimi AB. A phase I trial of immunosuppression with anti-ICAM-1 (CD54) mAb in renal allograft recipients. *Transplantation* 1993; **55**: 766–773.
40. Huang S, Paulauskis JD, Godleski JJ, Kobzik K. Expression of macrophage inflammatory protein-2 and KC mRNA in pulmonary inflammation. *American Journal of Pathology* 1992; **141**: 981–988.
41. Hughes BJ, Hollers JC, Crockett-Torabi E, Smith CW. Recruitment of CD11b/CD18 to the neutrophil surface and adherence-dependent cell locomotion. *Journal of Clinical Investigation* 1992; **90**: 1687–1696.
42. Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 1992; **69**: 11–25.
43. Inauen W, Granger DN, Meininger CJ, Schelling ME, Granger HJ, Kvietys PR. An in vitro model of ischemia reperfusion-induced microvascular injury. *American Journal of Physiology* 1990; **259**: G134–G139.
44. Jones DA, McIntire LV, Smith CW, Picker LJ. A 2-step adhesion cascade for T-cell endothelial-cell interactions under flow conditions. *Journal of Clinical Investigation* 1994; **94**: 2443–2450.
45. Jones DA, Smith CW, McIntire LV. Effects of fluid shear stress on leukocyte adhesion to endothelial cells. In: Granger DN, Schmid-Sonbein GW, eds. *Physiology and Pathophysiology of Leukocyte Adhesion*. New York: Oxford University Press, 1995, 148–168.
46. Kansas GS, Ley K, Munro JM, Tedder TF. Regulation of leukocyte rolling and adhesion to high endothelial venules through the cytoplasmic domain of L-selectin. *Journal of Experimental Medicine* 1993; **177**: 833–838.
47. Kapelanski DP, Iguchi A, Niles SD, Mao HZ. Lung reperfusion injury is reduced by inhibiting a CD18-dependent mechanism. *Journal of Heart and Lung Transplant* 1993; **12**: 294–306.
48. Kelner GS, Kennedy J, Bacon KB, Kleyensteuber S, Largaespada DA, Jenkins NA, X Copeland NG, Bazan JF, Moore KW, Schall TJ, Zlotnik A. Lymphotactin—a cytokine that represents a new class of chemokine X. *Science* 1994; **266**: 1395–1399.
49. Kubatiev A, Rudko I, Ermolenko V. Complement activation and neutrophil aggregation changes during hemodialysis. *International Journal of Clinical Pharmacology Research* 1993; **13**: 293–299.
50. Kuijpers TW, Mul EP, Blom M, Kovach NL, Gaeta FC, Tollefson V, Elices MJ, Harlan JM. Freezing adhesion molecules in a state of high-avidity binding blocks eosinophil migration. *Journal of Experimental Medicine* 1993; **178**: 279–284.
51. Lasky LA. Selectins: Interpreters of cell-specific carbohydrate information during inflammation. *Science* 1992; **258**: 964–969.
52. Lichtman AH, Segal GB, Lichtman MA. The role of calcium in lymphocyte proliferation (an interpretive review). *Blood* 1983; **61**: 413–422.
53. Lo SK, Lee S, Ramos RA, Lobb R, Rosa M, Chi-Rosso G, Wright SD. Endothelial-leukocyte adhesion molecule 1 stimulates the adhesive activity of leukocyte integrin CR3 (CD11b/CD18, Mac-1, αβ) on human neutrophils. *Journal of Experimental Medicine* 1991; **173**: 1493–1500.
54. Lukacs NW, Kunkel SL, Strieter RM, Warmington K, Chensue SW. The role of macrophage inflammatory protein 1alpha in *Schistosoma mansoni* egg-induced granulomatous inflammation. *Journal of Experimental Medicine* 1993; **177**: 1551–1560.
55. Lukacs NW, Strieter RM, Kunkel SL. Leukocyte infiltration in allergic airway inflammation. *American Journal of Respiratory Cell and Molecular Biology* 1995; **13**: 1–6.
56. Marcus AJ. Thrombosis and inflammation as multicellular processes. *Seminars in Hematology* 1994; **31**: 261–269.
57. Marty C, Misset B, Tamion F, Fitting C, Carlet J, Cavaillon JM. Circulating IL-8 in patients with multiple organ failure of septic and non-septic origin. *Critical Care Medicine* 1994; **22**: 673–679.
58. Montrucchio G, Alloatti G, Mariano F, Comino A, Cacace G, Polloni R, De Filippi PG, Emanuelli G, Camussi G. Role of platelet-activating factor in polymorphonuclear neutrophil recruitment in reperfused ischemic rabbit heart. *American Journal of Pathology* 1993; **142**: 471–474.
59. Mulligan MS, Paulson JC, De Frees S, Zheng Z-L, Lowe JB, Ward PA. Protective effects of oligosaccharides in P-selectin-dependent lung injury. *Nature* 1993; **364**: 149–151.
60. Mulligan MS, Watson SR, Fennie C, Ward PA. Protective effects of selectin chimeras in neutrophil-mediated lung injury. *Journal of Immunology* 1993; **151**: 6410–6417.
61. Murphy PM. The molecular biology of leukocyte chemoattractant receptors. *Annual Review of Immunology* 1994; **12**: 593–633.
62. Nash GB, Christopher B, Morris AJR, Dormandy JA. Changes in the flow properties of white blood-cells after acute myocardial infarction. *British Heart Journal* 1989; **62**: 329–334.
63. Nash GB, Morland C, Sheikh S, Buttrum SM, Lalor P. Adhesion between platelets and leukocytes: rheology, mechanisms and consequences. *Progress in Applied Microcirculation* 1996; (in press).
64. Nash GB, Thomas PRS, Dormandy JA. Abnormal flow properties of white blood-cells in patients with severe ischemia of the leg. *British Medical Journal* 1988; **296**: 1699–1701.
65. Neumann FJ, Waas W, Diehm C, Weiss T, Haupt HM, Zimmermann R, Tillmanns H, Kubler W. Activation and decreased deformability of neutrophils after intermittent claudication. *Circulation* 1990; **82**: 922–929.
66. Newman W, Beall LD, Carson CW, Hunder GG, Graber N, Randhawa ZI, Gopal TV, Wiener-Kronish J, Matthay MA. Soluble endothelial-leukocyte adhesion molecule-1 (ELAM-1) is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. *Journal of Immunology* 1993; **150**: 6440–654.
67. Oppenheim JJ, Zachariae COC, Mukaida N, Matsushima K. Properties of the novel proinflammatory supergene "intercrine" cytokine family. *Annual Review of Immunology* 1991; **9**: 617–648.
68. Palabrica T, Lobb R, Furie BC, Aronowitz M, Benjamin C, Hsu Y-M, Sajer SA, Furie B. Leukocyte accumulation promoting fibrin deposition is mediated in vivo by P-selectin on adherent platelets. *Nature* 1992; **359**: 848–850.
69. Pattison J, Nelson PJ, Huie P, von Leuttichau I, Farshid G, Sibley RK, Krensky AM. RANTES chemokine expression in cell-mediated transplant rejection of the kidney. *Lancet* 1994; **343**: 209–211.
70. Perry I, Buttrum SM, Nash GB. Effect of activation on adhesion of flowing neutrophils to cultured endothelium—time-course and inhibition by a calcium-channel blocker (nitrendipine). *British Journal of Pharmacology* 1993; **110**: 1630–1634.
71. Phillips DR, Charo IF, Scarborough RM. GPIIb–IIIa: the responsive integrin. *Cell* 1991; **65**: 359–362.
72. Picker LJ. Control of lymphocyte homing. *Current Opinions in Immunology* 1994; **6**: 394–406.
73. Picker LJ, Treer JR, Ferguson-Darnell B, Collins PA, Buck D, Terstappen LW. Control of lymphocyte recirculation in man: I. Differential regulation of the peripheral lymph node homing receptor L-selectin on T cells during the virgin to memory cell transition. *Journal of Immunology* 1993; **150**: 1105–1121.
74. Pober JS, Cotran RS. What can be learned from the expression of endothelial adhesion molecules in tissues? *Laboratory Investigations* 1991; **64**: 301–305.
75. Rainger GE, Fisher A, Shearman C, Nash GB. Adhesion of flowing neutrophils to cultured endothelial-cells after hypoxia and reoxygenation in-vitro. *American Journal of Physiology—Heart and Circulatory Physiology* 1995; **38**: H1398–H1406.
76. Rainger GE, Nash GB. Rapid and sequential signalling by interleukin-8 and PAF induce capture and then migration of rolling neutrophils. *Blood Coagulation and Fibrinolysis* 1995; **6**: 595 (abstract).
77. Rathanaswami P, Hachicha M, Sadick M, Schall TJ, McColl SR. Expression of the cytokine RANTES in human rheumatoid synovial fibroblasts. Differential regulation of RANTES and interleukin-8 genes by inflammatory cytokines. *Journal of Biological Chemistry* 1993; **268**: 5834–5839.
78. Rinder HM, Bonan JL, Rinder CS, Ault KA, Smith BR.

Dynamics of leukocyte platelet adhesion in whole blood. *Blood* 1991, **75**: 388–393.

79. Rot A. Endothelial cell binding of NAP-1/IL-8: role in neutrophil emigration. *Immunology Today* 1992; **13**: 291–294.
80. Rothlein R, Mainolfi EA, Czajkowski M, Marlin SD. A form of circulating ICAM-1 in human serum. *Journal of Immunology* 1991; **147**: 3788–3793.
81. Schall TJ. Biology of the RANTES/SIS cytokine family. *Cytokine* 1991; **3**: 165–183.
82. Schall TJ, Bacon K, Camp RD, Kaspari JW, Goeddel DV. Human macrophage inflammatory protein alpha (MIP-1alpha) and MIP-1beta chemokines attract distinct populations of lymphocytes. *Journal of Experimental Medicine* 1993; **177**: 1821–1826.
83. Schall TJ, Bacon K, Toy KJ, Goeddel DV. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature* 1990; **347**: 669–671.
84. Schleimer RP, Sterbinsky SA, Kaiser J, Bickel CA, Klunk DA, Tomioka K, Newman W, Luscinskas FW, Gimbrone MA Jr, McIntyre BW, Bochner BS. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium: association with expression of VCAM-1. *Journal of Immunology* 1992; **148**: 1086–1092.
85. Schmid-Schonbein GW, Engler RL. Granulocytes as active participants in myocardial ischaemia and infarction. *American Journal of Cardiovascular Pathology* 1987; **1**: 15–30.
86. Schmouder RL, Strieter RM, Walz A, Kunkel SL. Epithelial-derived neutrophil-activating factor-78 production in human renal tubule epithelial cells and in renal allograft rejection. *Transplantation* 1995; **59**: 118–124.
87. Seitz M, Loetscher P, Dewald B, Towbin H, Ceska M, Baggiolini M. Production of interleukin-1 receptor antagonist, inflammatory chemotactic proteins, and prostaglandin E by rheumatoid and osteoarthritic synoviocytes—regulation by IFN-gamma and IL-4. *Journal of Immunology* 1994; **152**: 2060–2065.
88. Sekido N, Mukaida N, Harada A, Nakanishi I, Watanabe Y, Matsushima K. Prevention of lung perfusion injury in rabbits with a monoclonal antibody to interleukin-8. *Nature* 1993; **365**: 654–657.
89. Selby C, Drost E, Wraith PK, Macnee W. In vivo neutrophil sequestration within lungs of humans is determined by in vitro filterability. *Journal of Applied Physiology* 1991; **71**: 1996–2003.
90. Sheikh S, Nash GB. Continuous activation and deactivation of integrin CD11b/CD18 during de novo expression enables rolling neutrophils to immobilise on platelets. *Blood* 1996; (in press).
91. Shimizu Y, Newman W, Gopal TV, Horgan KJ, Graber N, Beall LD, van Seventer GA, Shaw S. Four molecular pathways of T cell adhesion to endothelial cells: roles of LFA-1, VCAM-1 and ELAM-1 and changes in pathway hierarchy under different activation conditions. *Journal of Cell Biology* 1991; **113**: 1203–1212.
92. Shimizu Y, Shaw S, Graber N, Gopal TV, Horgan KJ, van Seventer GA, Newman W. Activation-independent binding of human memory T cells to ELAM-1. *Nature* 1991; **349**: 799–802.
93. Simon SI, Burns AR, Taylor AD, Gopalan PK, Lynam EB, Sklar LA, Smith CW. L-selectin (cd62l) cross-linking signals neutrophil adhesive functions via the mac-1 (cd11b/cd18) beta(2)-integrin. *Journal of Immunology* 1995; **155**: 1502–1514.
94. Simon SI, Rochon YP, Lynam EB, Smith CW, Anderson DC, Sklar LA. Beta-2-integrin and L-selectin are obligatory receptors in neutrophil aggregation. *Blood* 1993; **82**: 1097–1106.
95. Sousa AR, Lane SJ, Nakhosteen JA, Yoshimura T, Lee TH, Poston RN. Increased expression of the monocyte chemoattractant protein-1 in bronchial tissue from asthmatic subjects. *American Journal of Respiration—Cell and Molecular Biology* 1994; **10**: 142–147.
96. Springer TA. Adhesion receptors of the immune system. *Nature* 1990; **346**: 425–434.
97. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* 1994; **76**: 301–314.
98. Standiford TJ, Kunkel SL, Lukacs NW, Greenberger MJ, Danforth JM, Kunkel RG, Strieter RM. Macrophage inflammatory protein-1-alpha mediates lung leukocyte recruitment, lung capillary leak, and early mortality in murine endotoxemia. *Journal of Immunology* 1995; **155**: 1515–1524.
99. Stutman O. Postthymic T-cell development. *Immunology Reviews* 1986; **91**: 159–194.
100. Tanaka Y, Adams DH, Hubscher S, Hirano H, Siebenlist U, Shaw S. T-cell adhesion induced by proteoglycan-immobilized cytokine MIP-1β. *Nature* 1993; **361**: 79–82.
101. Tanaka Y, Adams DH, Shaw S. Proteoglycan on endothelial cells presents adhesion-inducing cytokines to leukocytes. *Immunology Today* 1993; **14**: 111–114.
102. Tanaka Y, Albelda SM, Horgan KJ, van Seventer GA, Shimizu Y, Newman W, Hallam J, Newman PJ, Buck CA, Shaw S. CD31 expressed on distinctive T cell subsets is a preferential amplifier of β1 integrin-mediated adhesion. *Journal of Experimental Medicine* 1992; **176**: 245–253.
103. Taub DD, Conlon K, Lloyd AR, Oppenheim JJ, Kelvin DJ. Preferential migration of activated human CD4+ and CD8+ T cells in response to MIP-1α and MIP-1β. *Science* 1993; **260**: 355–358.
104. Tozeren A, Ley K. How do selectins mediate leukocyte rolling in venules? *Biophysics Journal* 1992; **63**: 700–709.
105. Tuomanen EI, Prasad SM, George JS, Hoepelman AIM, Ibsen P, Heron I, Starzyk RM. Reversible opening of the blood–brain barrier by anti-bacterial antibodies. *Proceedings of the National Academy of Sciences, USA* 1993; **90**: 7824–7828.
106. Weiss SJ. Tissue destruction by neutrophils. *New England Journal of Medicine* 1989; **320**: 365–376.
107. Welbourn CRB, Goldman G, Paterson IS, Valeri CR, Shepro D, Hechtman HB. Pathophysiology of ischemia reperfusion injury—central role of the neutrophil. *British Journal of Surgery* 1991; **78**: 651–655.
108. Williams AF. Out of equilibrium. *Nature* 1991; **352**: 473–474.
109. Winn RK, Sharar SR, Vedder NB, Harlan JM. The contribution of adherent leukocytes to septic shock. In: Granger DN, Schmid-Schonbein GW, eds. *Physiology and Pathophysiology of Leukocyte Adhesion*. New York: Oxford University Press, 1995: 381–392.
110. Winn RK, Sharar SR, Vedder NB, Harlan JM. Leukocyte and endothelial adhesion molecules in ischaemia reperfusion injuries. *Ciba Foundation Symposium* 1995; **189**: 63–76.
111. Witt DP, Lander AD. Differential binding of chemokines to glycosaminoglycan subpopulations. *Current Biology* 1994; **4**: 394–400.
112. Worthen GS, Schwab B, Elson EL, Downey GP. Mechanics of stimulated neutrophils—cell stiffening induces retention in capillaries. *Science* 1989; **245**: 183–186.
113. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha-4beta1integrin. *Nature* 1992; **356**: 63–66.
114. Zimmermann BJ, Anderson DC, Granger DN. Neuropeptides promote neutrophil adherence to endothelial cell monolayers. *American Journal of Physiology* 1992; **263**: 678–682.

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Molecular mechanisms of drug metabolism in the critically ill

G. R. PARK

Drugs are used in every critically ill patient. Despite this, our knowledge of how drugs behave in these patients has, until lately, been limited. It has been based on information obtained from animals, volunteers, relatively fit patients or others in a stable phase of a chronic disease. Ethical, logistical, financial and the confounding effects of disease have delayed the understanding of drug metabolism in this group of patients. Although these difficulties are now being overcome the advent of isolated cell systems and molecular biological techniques are answering questions that could not be answered by studying patients. Indeed, these techniques will not only help solve some of these problems, they will help prevent others with new drugs. Already drug interactions can be predicted before a drug is marketed. In addition, new drugs are now being designed not to use routes of elimination likely to fail in the critically ill.

Drug metabolism is not static but dynamic. It can be expected to change as the patient's condition worsens or changes. This is illustrated by one patient in septic shock who was given a continuous infusion of midazolam (fig. 1). At first there is a rapid increase in the concentration of midazolam, with little or no production of the metabolite because the enzymes are "sick". As his condition (and that of the enzymes) improves (day 4) metabolite appears in the blood. On day 13 he develops a nosocomial pneumonia and again the enzymes become "sick" and the production of metabolite is reduced [135].

Metabolism

Drugs are usually metabolized through several pathways, the aim being to change fat soluble, active, unexcretable drugs into water soluble, inactive drugs that are able to be excreted by the kidneys and in the bile.

Two phases of metabolism are usually involved. The first is phase I metabolism, that commonly involves the cytochromes P450 (CYP), performing reactions such as oxidation and hydroxylation. Other phase I reactions, involving other enzymes also occur (table 1).

The metabolites these enzymes produce may be less active or highly reactive and even toxic. For example, when paracetamol is metabolized by phase I metabolism, the metabolite, *N* acetyl-*p*-benzoquinone (NAPQI), causes hepatotoxicity. Usually the phase I metabolite is metabolized further by a phase II enzyme that conjugates it with another group such as glutathione, a glucuronide or a sulphide group. A typical example of a drug going through both phase I and phase II metabolism is midazolam. It is metabolized first to 1-hydroxy midazolam and then to 1-hydroxy midazolam glucuronide.

Some drugs are metabolized mostly by phase II metabolism. An example of this is morphine, that is metabolized to morphine-3 glucuronide (M-3G) and morphine-6 glucuronide (fig. 2).

It should be noted that many drugs have several pathways. Indeed, drugs may switch between pathways. In one study [71] rats were infected with malaria and then given low and high doses of paracetamol. Compared with uninfected rats there was little change in the clearance of paracetamol, but there was a decrease in glucuronidation compensated for by an increase in sulphation. At high doses sulphation was saturated and clearance reduced.

Cytochromes P450 and other phase I enzymes are generally present in smaller amounts than phase II enzymes and they are more affected by disease. If they are reduced in amount the metabolite for phase II metabolism will not be made and the drug will not be metabolized. Thus, the amount and function of phase I enzymes are usually the rate limiting step in drug metabolism.

Cytochromes P450 are a family of haemoproteins. About 25 have been described in humans: they are characterized by their amino acid homology. Families are identified by an Arabic number and have at least 40% amino acid homology. The subfamily is identified by a capital letter and has at least 55% amino acid homology [106]. The gene product is identified by a further Arabic number. This nomenclature has superseded the classification based on substrate specificity. It allows recognition that cyclosporin oxidase and nifedipine oxidase are an identical enzyme; cytochrome P450 3A4.

The cytochromes P450 are ubiquitous. The highest *concentrations* of these enzymes are found in the nose (where they break down the amines that cause smell) and in the adrenal gland (where they produce steroids). The greatest *mass* is found in the liver. They have many functions besides the metabolism of xenobiotics. They are important in the regulation of the body, making steroids of all types. Furthermore,

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Key words

Metabolism, drug. Structure, molecular. Enzymes, cytochrome P450. Analgesics opioid.

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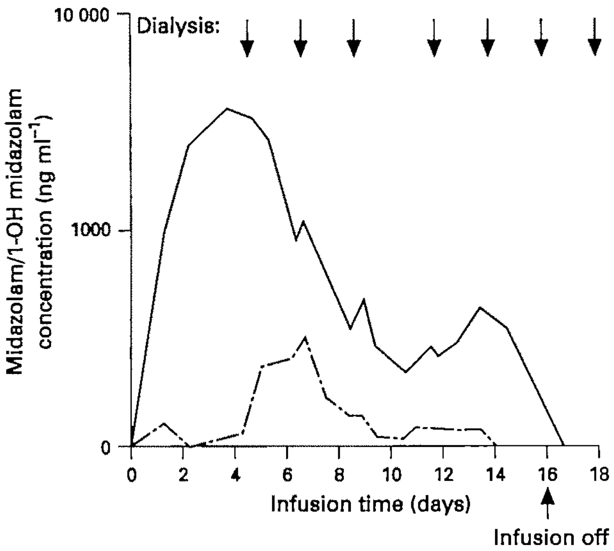

Figure 1 Changing enzyme function in the critically ill. When the patient is first given midazolam it is not metabolized, so there is no metabolite (1-hydroxy midazolam). As he improves so metabolite appears. Later he develops a nosocomial pneumonia and again fails to metabolize midazolam [135]. (——), Midazolam; (–·–·–); 1-hydroxy (1-OH) midazolam.

Table 1 Some enzymes performing phase I oxidation, other than cytochromes P450 [52]

Alcohol dehydrogenase
Aldehyde dehydrogenase
Alkylhydrazine oxidase
Amine oxidases
Aromatases
Xanthine oxidase

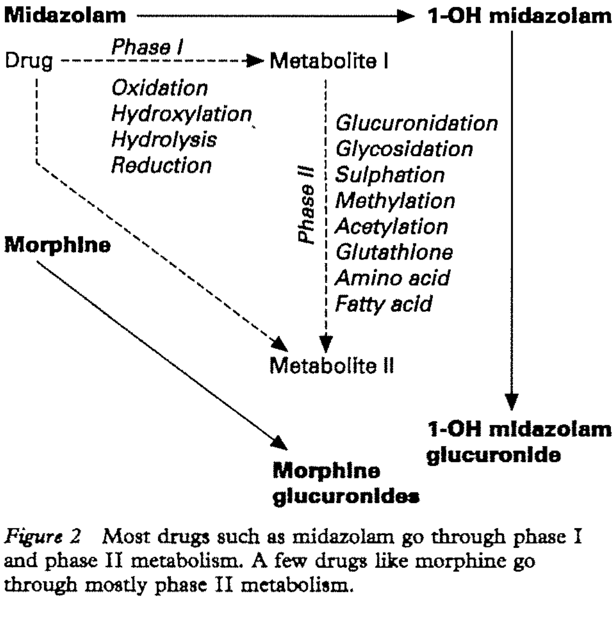

Figure 2 Most drugs such as midazolam go through phase I and phase II metabolism. A few drugs like morphine go through mostly phase II metabolism.

their study is of great importance in understanding carcinogenesis since, for example, it is these enzymes that produce carcinogens from cigarette smoke.

Three enzymes are of major importance in understanding drug metabolism for anaesthetists, others are shown in table 2. Cytochrome P450 2D6 has polymorphic expression and does not function in 10% of the population. Cytochrome P450 2E1 produces many reactive metabolites. Mention has already been made of paracetamol, but this cytochrome also metabolizes volatile agents again producing reactive metabolites. Cytochrome P450 3A4, comprising about 60% of all of the cytochromes in the body, metabolizes many drugs used in the critically ill patient.

Some of the drugs used in the critically ill and the enzymes that metabolize them are shown in table 3.

A third group of enzymes is becoming increasingly important for drug metabolism. These are the blood and tissue esterases. The importance of variations in butyryl cholinesterase (pseudocholinesterase) has been appreciated for some time because of its role in metabolizing suxamethonium. Currently, drugs are being designed to go either through butyryl cholinesterase or other esterases similar to it. Mivacurium, a non-depolarizing neuromuscular blocking agent is also metabolized by butyryl cholinesterase and suffers from the same difficulties in metabolism as suxamethonium [111].

Remifentanil, a new opioid, is metabolized by many esterases found both in the blood and elsewhere. This new opioid, because it is metabolized by so many different blood and tissue esterases, is unlikely to be affected by disease or genetic variation, as are suxamethonium and mivacurium. This also makes remifentanil's metabolism independent of liver function. Studies during the anhepatic period of liver transplantation have shown its elimination to be normal [105].

Since the body metabolizes many thousands of compounds every day and has far fewer enzymes, each enzyme metabolizes many substrates. Only very rarely, if ever, will one enzyme only metabolize one substrate.

Changes in enzyme function in the critically ill

Many things change enzyme function. Some of these are shown in figure 3.

Mechanisms for enzyme induction are poorly understood, unlike inhibition, which has been better studied. Generally, inhibition is a fast process while induction is slow. This is because induction results in an increased amount of enzyme in the cell; it usually takes about 24–48 h for this to occur [9]. Some of the mechanisms controlling the amount of enzyme are shown in figure 4.

Some of the common cytochrome P450 inducers and inhibitors are shown in table 4.

Inhibition is usually quick, occurring sometimes after one dose of the inhibitor. It may occur because of changes in the expression of the enzyme, changes in the environment of the cell or because of direct interference with the enzyme itself. For example, there may be substrate competition, illustrated by the combination of erythromycin and midazolam, commonly used in the critically ill patient. The erythromycin prevents the metabolism of midazolam by cytochrome P450 3A4 [67], leading to prolonged coma. There may also be metabolite inhibition of an

Table 2 Various cytochromes P450 (from ref. [29] and elsewhere)

CYP 1A1	This is not expressed constitutively in the liver. It is induced by a variety of substances including omeprazole and cigarette smoking and may be implicated in causing cancer. Other environmental changes may also induce it.
CYP 1A2	Expressed constitutively. Its expression may also be changed by diet or other habits.
CYP 2A6	Constitutively expressed. It is responsible for 7-hydroxylation of steroids and cholesterol to bile acids.
CYP 2C8-2C9	Constitutively expressed. Responsible for the metabolism of tolbutamide, phenytoin (2C19), diazepam and the oxicam NSAID.
CYP 2D6	This cytochrome is subject to polymorphic expression. Debrisoquine, morphine, its analogues and β-blockers are metabolized by it.
CYP 2E1	Constitutively expressed. It metabolizes small molecules including volatile anaesthetic agents, alcohol and other hydrocarbons. This cytochrome is found in the centrilobular region of the liver, the most hypoxic area.
CYP 3A4	Of all the CYP this is the most prolific in human liver. It also metabolizes several drugs commonly used in critically ill patients.
CYP 4A	It is important in many endogenous control pathways. Its expression is controlled by dietary status especially, fats.

enzyme, such as is caused by the antidepressant nortriptyline [104]. Its phase I metabolite inhibits the enzyme that produces it. More recently Cheng and colleagues have shown that propofol may inactivate cytochromes P450 [28]. The importance of this has not yet been shown in humans, but if their *in vitro* results apply to humans then delay and elimination of several drugs might be expected. These and other mechanisms are shown in table 5.

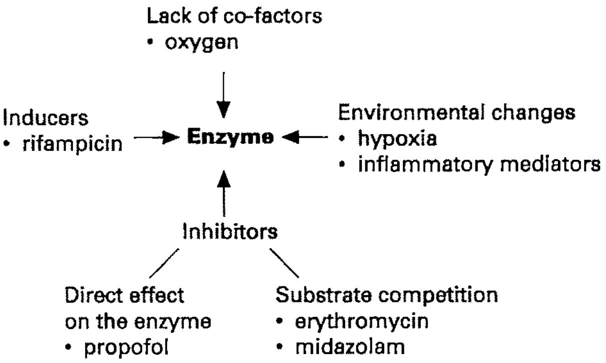

Figure 3 Some of the factors that may change enzyme function.

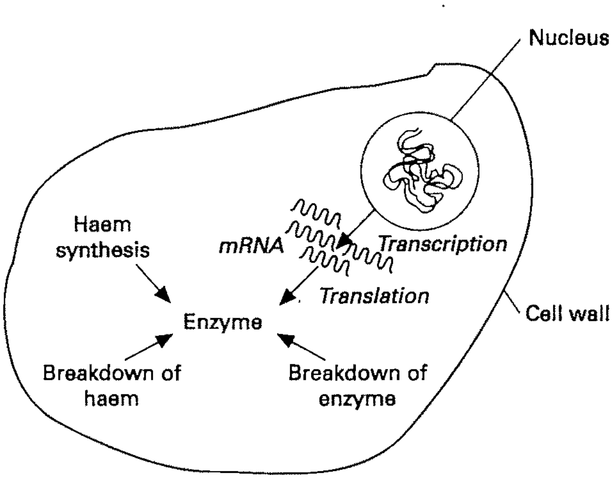

Figure 4 Some of the sites in the cell where different factors may control the amount of enzyme present in the cell [33, 52]. Changes in all of these steps have been described for induction, but not inhibition, of the enzyme.

GENETIC FACTORS

Although interspecies differences in the metabolism of drugs are known about [11] differences within species are less well recognized. However, these can be just as pronounced. In the mouse, sleeping time after hexobarbitone administration varies from 18 (SD 4) min in the SWR/HeN mouse to 48 (4) min for the A/NL mouse, purely because of the variation in enzyme function [52].

In humans even more striking differences exist for the metabolism of suxamethonium. This is metabolized by butyryl cholinesterase which is under the control of several genes. The commonest gene is E_1^u. The various phenotypes and most genotypes can be differentiated on the basis of inhibition of cholinesterase by dibucaine (E_1^a) and fluoride (E_1^f). The silent gene (E_1^s) occurs when the organism is in the homozygous state and so cannot be inhibited. The heterozygote state has normal dibucaine and fluoride inhibition, but reduced cholinesterase function (table 6).

Another important enzyme that is subject to genetic polymorphism is CYP 2D6. Several variants of this enzyme have also been described [69]. Originally, debrisoquine metabolism was noted to be affected by the abnormalities of this enzyme. However, this enzyme also metabolizes codeine to morphine. Because of this, in the 10% of the population who lack functioning CYP 2D6, codeine may be a poor analgesic.

Enzyme changes in the critically ill

Enzymes tend to be thought of as "black boxes". The drug goes in and the metabolite comes out, but enzymes are proteins and just as plasma concentrations of albumin decrease and those of alpha-1 acid glycoprotein increase in response to stress, so intracellular concentrations of enzymes also change.

There is now an increasing amount of information about how enzymes change in response to *one*

Table 3 Some of the drugs used in the critically ill and the cytochromes P450 that metabolize them [92]

	CYP1A	CYP2C	CYP2D6	CYP3A		CYP1A	CYP2C	CYP2D6	CYP3A		CYP1A	CYP2C	CYP2D6	CYP3A
Mefenamic acid		■			Digoxin				■	Pancuronium		■		
Valproic acid		■	■	■	Erythromycin				■	Paracetamol	■			■
Alfentanil				■	Fentanyl				■	Pethidine				■
Amitriptyline			■	■	Fluconazole				■	Phenacetin	■			
Bupivacaine				■	Glibenclamide		■		■	Phenformin			■	
Carbamazepine				■	Haloperidol			■	■	Phenobarbitone		■		
Chloramphenicol				■	Imipramine		■	■	■	Phenylbutazone		■		■
Chlorpromazine			■	■	Itraconazole				■	Phenytoin		■		■
Chlorpropamide		■		■	Ketoconazole				■	Prednisolone				■
Cyclosporin				■	Lignocaine				■	Propranolol		■	■	■
Cimetidine	■			■	Methoxyflurane			■		Theophylline	■			■
Codeine			■		Metoprolol			■	■	Thiopentone		■		
Cortisol				■	Methylprednisolone				■	Thioridazine			■	■
Cyclophosphamide		■		■	Metronidazole				■	Tolbutamide		■		■
Dantrolene				■	Midazolam				■	Tramadol			■	■
Debrisoquine			■		Nifedipine				■	Verapamil				■
Dexamethasone				■	Nimodipine				■	Warfarin		■		■
Diazepam		■		■	Omeprazole		■							
Diclofenac		■			Ondansetron			■	■					

Table 4 Cytochromes P450 (A) inducers and (B) inhibitors [92]

(A) Enzyme inducers:

	CYP1A	CYP2C	CYP2D6	CYP3A		CYP1A	CYP2C	CYP2D6	CYP3A
Ethacrynic acid		■			Ketoconazole		■		■
Mefenamic acid		■			Lansoprazole		■		
Nalixidic acid		■			Methyldopa		■		
Amiodarone	■	■	■	■	Methylprednisolone				■
Cyclosporin				■	Metronidazole		■		■
Cimetidine			■	■	Omeprazole		■		
Dexamethasone				■	Paracetamol		■		
Disopyramide				■	Phenylbutazone		■		
Erythromycin				■	Phenytoin		■		
Fluconazole		■	■	■	Propofol				■
Haloperidol			■		Propranolol				■
Isoniazid				■	Thyroxine			■	
Itraconazole		■		■	Verapamil				■

(B) Enzyme inhibitors

	CYP1A	CYP2C	CYP2D6	CYP3A		CYP1A	CYP2C	CYP2D6	CYP3A		CYP1A	CYP2C	CYP2D6	CYP3A
Mefenamic acid		■			Fluconazole		■	■	■	Paracetamol		■		
Nalixidic acid		■			Haloperidol			■		Pentoxifylline				■
Valproic acid		■		■	Isoniazid				■	Phenylbutazone		■		
Amiodarone	■	■	■	■	Ketoconazole		■		■	Propofol				■
Chloramphenicol		■		■	Lansoprazol		■			Propranolol				■
Chlorpromazine			■		Methylprednisolone				■	Ranitidine				■
Cyclosporin				■	Metronidazole		■		■	Salicylates		■		
Cimetidine			■	■	Miconazole		■		■	Tetracycline				■
Ciprofloxacin	■				Nicardipine				■	Thioridazine			■	
Dexamethasone				■	Nifedipine				■	Thyroxine				■
Erythromycin				■	Omeprazole		■			Verapamil				■

Table 5 Some of the mechanisms by which enzymes are inhibited [52]

Denaturation of enzyme
Lipid peroxidation
Covalent binding (suicide substrate)
Competition
Haem loss
Increased degradation

Table 6 Genetic abnormalities of butyryl cholinesterase (pseudocholinesterase) E_1^u = common gene, E_1^a = gene controlling plasma cholinesterase characterized by dibucaine inhibition, E_1^f = gene controlling plasma cholinesterase characterized by fluoride inhibition and E_1^s = silent gene. (From various sources [64, 77, 156])

	Dibucaine inhibition (%)	Fluoride inhibition (%)	Frequency normal population (%)
Inhibition of dibucaine:			
E_1^u, E_1^u	80–84	57–64	
E_1^u, E_1^a	45–75	45–53	4
E_1^a, E_1^a	14–27	17–32	> 0.5
Inhibition by fluoride:			
E_1^u, E_1^u	80–84	57–64	
E_1^u, E_1^f	72–81	41–57	
E_1^f, E_1^f	64–67	34–35	> 0.5
"Silent" gene:			
E_1^u, E_1^s	72–84	50–70	
	(Cholinesterase activity reduced)		
E_1^s, E_1^s	0	0	

stimulus. It is important to remember that usually several stimuli exist at the same time in each patient.

HYPOXIA

The liver is particularly sensitive to hypoxia because 70% of its blood supply is from the portal vein which has blood with a low oxygen content. The remaining 30% is from the hepatic artery. This leads to large differences in the oxygen supply in different parts of the liver. Those near the arterial supply having a high concentration of oxygen and others having a low concentration. These hepatocytes are especially sensitive to hypoxia. Small reductions in hepatic blood flow or blood oxygen concentration will result in these cells becoming ischaemic [138]. This explains the frequency with which ischaemic hepatitis is seen [53].

Oxygen is needed by the cell to metabolize drugs efficiently for several reasons. It is used to produce energy needed both for the reactions themselves and also to make the enzyme. Oxygen is also needed as a substrate for drug oxidation, as a terminal electron acceptor and for processes dependent on the oxidation equilibrium (redox potential of the cell).

Animal work shows that the lowest fractional concentration of inspired oxygen ($F\text{I}_{O_2}$) that a rat who has been given phenobarbitone to induce its enzymes can survive is 0.07. However, liver damage occurs at this concentration. At an $F\text{I}_{O_2}$ of 0.06 the rats start to die and in the survivors liver damage is greater. Although hepatocytes survive in oxygen tensions as low as 0.1 mm Hg ischaemic hepatocytes will not function normally [5] and oxygen tension of 2–10 mm Hg (3–14 μmol litre^{-1}) is needed for energy production.

Although a reduction in $F\text{I}_{O_2}$ will cause hypoxia so too will shock, because of the reduction in blood flow, and consequently oxygen, to the liver. Shock may result from many causes including trauma and myocardial infarction. Both are associated with a reduction in metabolic activity [48]. A German group [48] measured the amount of CYP from a needle biopsy in patients dying with and without shock after myocardial infarction. They also measured the steady state plasma concentration of lignocaine after an infusion. They found patients with shock had a higher plasma concentration (showing a reduced clearance) but the plasma concentration decreased when they were given dobutamine to increase cardiac output. Many mechanisms are involved in the decreased ability of shocked patients to metabolize drugs; a reduction in liver blood flow with resulting hepatic hypoxia is one of these.

Some enzymes are more tolerant of hypoxia than others. Those found in acinar zone 1 (sulphation) are less sensitive to hypoxia than those found in zone 3 (oxidation). Furthermore, cytochrome P450 2E1 is concentrated in the pericentral region of the lobule, the most hypoxic [150]. Thus changes in the oxygen gradients may be expected to change metabolic pathways for drugs metabolized by several enzymes [76].

The time taken for hypoxia to induce changes in drug metabolizing enzymes appears to be short. One study [35] found that rabbits exposed to a low $F\text{I}_{O_2}$ had changes in the ability of their liver enzymes, to metabolize theophylline within 8 h.

When we exposed isolated human hepatocytes in primary culture [117] to hypoxia for 4 days there was a 5–10-fold reduction in cytochrome P450 3A. This was not thought to be caused purely by cell asphyxia because cytochrome P450 2E1 was less affected. The mechanisms surrounding changes in the amount of enzyme in cells are poorly understood. However, substances, such as hypoxia inducible factor I, are being identified to be responsible for the transcription of the human erythropoietin gene [154]; and other similar factors may exist for other genes.

Studying the effects of acute hypoxia in intact animals is difficult because of the various compensatory changes that occur in the cardiovascular system. Increases in cardiac output and changes in regional blood flow will attempt to minimize the decrease in $F\text{I}_{O_2}$. To overcome these difficulties the isolated perfused liver has been used as a model to study the effects of hypoxia on the liver. In this model the concentration of oxygen, carbon dioxide and other nutrients can be controlled precisely. In addition, flow rates can also be changes. Using this model the importance of hypoxia on propranolol clearance has been shown [40, 41].

The changes caused by hypoxia will be worsened if drugs are given that increase cellular oxygen demands. One such group of drugs are the enzyme inducers. Becker and colleagues [14, 15] have shown the effect of inducing hepatic enzymes with phenobarbitone and the subsequent oxygen consumption of hepatocytes isolated from these animals. In the induced state, oxygen consumption increases with both volatile and i.v. anaesthetic agents. Some of these effects returned to normal when a cytochrome P450 inhibitor, metapyrone, was added to the incubates.

Current practice in the shocked patient is to restore cardiac output and improve oxygen delivery. A useful adjunct to this in the future might also be to choose drugs that do not increase cellular oxygen demands.

Liver preservation

Liver transplantation is becoming increasingly common and is one of the most extreme forms of hypoxia. How the liver metabolizes drugs immediately after it has been rendered anoxic, cooled and subjected to two operations has not been well studied. We have studied the metabolism of morphine [136], alfentanil [137] and midazolam [134], and others have looked at glucuronidation [152] and shown that they are metabolized almost normally. Still other workers have studied antipyrine [96]. In one study in rats the ability of livers removed and then stored using hypothermic preservation were compared by their ability to metabolize morphine, fentanyl and vecuronium in livers removed and studied immediately. No difference between the two groups could be found [80]. Thus, the hypoxic insult to the liver caused by transplantation does not appear to cause significant damage to the enzymes.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

This term is used to describe the body's response to various injuries [21] and is discussed elsewhere. SIRS affects most of the body, rather than a single organ. Inflammation is an essential part, sepsis with positive microbiological cultures is not essential.

In rats, experimentally induced inflammation has been shown to depress drug metabolism; however this is not reversed by anti-inflammatory agents [13]. Many inflammatory mediators have been described. The ones that are known to have an effect on drug metabolism are interleukin 1(IL-1) [1, 45, 51, 88, 145], interleukin 6 (IL-6) [1], tumour necrosis factor [1] and interferon [31, 32, 38, 50, 99, 102, 118, 125]. The release of many of these may be triggered by endotoxin, itself an important cause of changes in drug metabolism [37, 51, 101, 128, 132].

The inflammatory mediators appear to be essential for survival after infections. When mice were bred to be deficient in the IL-6 gene, they were unable to control infections with vaccinia viruses and *Listeria monocytogenes* [85]. Infecting mice with *Listeria monocytogenes* reduces the expression of some cytochromes P450 and their associated mRNA, taking 96 h to return to normal [6]. Infections release endoxin, and 15 years ago Egawa and colleagues [37] showed that the plasma of mice given endotoxin contained a substance that reduced the amount of cytochrome P450 and its activity. Morgan [101] also showed that in rats given endotoxin there was a reduction in liver cytochrome P450 and also in mRNA. However, a variety of other mechanisms maintained the enzyme, resulting in a proportionally lower reduction in protein than in mRNA. Others have shown similar changes after mice were given IL-1 [132].

Table 7 Effects of cytokines on the expression of some phase I enzymes. (IL = interleukin, TNF_α = tumour necrosis factor; IFγ = interferon.) (Adapted from ref. [1])

	IL-1β	IL-4	IL-6	TNFα	IFγ
1A1	⇓	⇓	⇓	⇓	⇓
2C	⇓	⇓	⇓	⇓	⇔
2E1	⇓	⇑^{5x}	⇓	⇓	⇓
3A	⇓	⇔	⇓	⇓	⇔
Epoxide hydrolase	⇓	No data	⇓	⇓	⇔

Information about human responses to individual inflammatory mediators is limited. Most of the information has been gained from isolated, human hepatocytes grown in primary culture. We used this method to show that serum from five critically ill patients (APACHE score [82] > 15) contains a substance that interferes with the metabolism of progesterone [113, 117]. Since it was unclear whether the serum might be affecting expression of the enzyme in the cells or having a direct inhibitory effect on the enzyme, we did a further study. In this we isolated microsomes (part of the endoplasmic reticulum) containing the cytochromes P450. Midazolam (a CYP 3A4 substrate [87]) was then incubated with the microsomes and serum. Again, the serum was shown to have an inhibitory effect [115]. Although this might explain our earlier observation suggesting the serum contained a substrate that directly inhibits the enzyme, Abdel Razzik and colleagues [1] in Paris, using human hepatocytes showed the mostly depressant effects of cytokines on phase I enzymes (table 7).

Thus it would appear that serum from critically ill patients may change drug metabolism by two mechanisms. First, it may contain an enzyme inhibitor. Second, it contains cytokines that may reduce the expression of cytochromes P450.

The Parisian group also showed interferon to have a depressant effect on the expression of cytochromes P450. Viral illness is known to depress drug metabolism [27] and this effect is probably caused by interferon [38, 99, 102]. Interferon may exert its effect in three possible ways. It may cause release of a second mediator, such as IL-1. Alternatively, interferon may induce xanthine oxidase, which increases the amount of free radicals present and may interfere with normal cell function [50]. Finally, interferon may enhance haem turnover, reducing the amount of cytochromes P450 present [38, 100].

TEMPERATURE

Most chemical reactions are sensitive to temperature, going faster as the temperature increases and slower with a decrease in temperature. Despite this, fever does not increase the rate of metabolism of drugs.

Antipyrine (a substance metabolized by at least two cytochromes P450) metabolism was reduced in volunteers who had a fever induced with a pyrogen [39]. Similarly, the metabolism of quinine (also a cytochrome P450 substrate) is decreased during acute malaria and steroid induced fever [149]. This paradoxical finding may be explained by the cause of the fever. Both infections and pyrogens will cause the release of inflammatory mediators. These will reduce the expression and activity of the enzymes responsible for the metabolism of antipyrine and quinine.

Acute hypothermia, induced during cardiopulmonary bypass, has been shown to reduce the clearance of esmolol [72]. These patients were given esmolol by continuous infusion during bypass and when the patient was cooled plasma concentration of esmolol increased, showing a reduction in clearance. Acute hypothermia caused by cardiopulmonary bypass may have more predictable effects on drug metabolism than hyperthermia because it would not be expected to release inflammatory mediators, with their own effects on enzymes. Furthermore, esmolol is metabolized by red cell esterases, rather than cytochromes P450, and these enzymes may be more temperature dependent.

STRESS

Non-traumatic stress has been shown to reduce enzyme function. Pollack and colleagues [120] studied rats exposed to a variety of stresses over 21 days. These included exposure to flashing lights, rocking their cages, food deprivation, isolation and swimming in cold water for 24 h (all, except the last, are remarkably similar to the stresses to which the critically ill are sometimes exposed!). Afterwards they measured the ability of the rats to eliminate antipyrine and hepatic blood flow. Both were decreased.

The reduction in antipyrine clearance cannot be explained merely by the reduction in liver blood flow, since antipyrine is not a high extraction drug and therefore solely dependent on liver blood flow. The increase in circulating catecholamines caused by stress probably decreased liver blood flow. This may, in turn, cause hepatic hypoxia causing a reduction in the enzymes metabolizing antipyrine.

SEX

Male and female rats behave differently when exposed to endotoxin. Each has specific sex-linked enzymes; in the male there is a 35% reduction in CYP 2C11, while in the female only a 17% decrease in CYP 2C12 after endotoxin. The female also shows the initial change and recovers faster than the male [101]. Whether such changes occur in humans is unknown. Little attention has been paid to difference in enzyme expression between men and women, although we have shown a difference in the expression of CYP 3A in liver tissue from organ donors [147].

DIET

Most critically ill patients have an abnormal diet. A change in diet, deficiencies or excesses of a variety of dietary components, is associated with abnormal enzyme function [75, 78, 79, 86, 119, 139, 158, 159] Vitamin C deficiency in guineapigs is associated with a decrease in certain cytochromes P450 [78]. Although scurvy is rare, lack of other vitamins and trace elements, which probably occurs regularly in the critically ill, may result in similar changes.

High fat diets also change cytochrome P450 expression. Parenteral nutrition using large amounts of fat has been shown to increase the oxidation of antipyrine [23]. One potential mechanism for this has been shown in rats fed on a variety of diets, one of which contained excess fat. These rats had an increase in cytochrome P450 2E1, which was associated with an increase in its mRNA. The cause of the increased mRNA was thought to be because the fat stimulated release of growth hormone, in turn changing gene transcription [159].

Starvation and malnutrition cause further changes [86, 139, 159], in particular an increase in cytochrome P450 2E1 [75]. Interestingly, this change may be blocked by the sedative, chlormethiazole [97].

ENDOCRINE DISEASE

Endocrine disease is common in the critically ill, but is poorly recognized. It may be the cause of admission to the intensive care unit; such an example is diabetic ketoacidosis. Also, drugs may also cause it—Addison's disease after etomidate (a potent cytochrome P450 inhibitor) [89, 91] and giving steroids are examples.

Diabetes mellitus is a common disease and for many years changes in the metabolic potential of these patients has been known [12]. However, these changes are only seen in patients with insulin-dependent diabetes and not those patients with type 2 diabetes. The reasons behind this were unclear. Changes in growth hormone and glucagon secretion had been suggested. A French group has shown that insulin itself changes the amount of cytochromes P450 present in isolated hepatocytes by decreasing the half-life of mRNA [34].

Corticosteroids will also change the expression of drug metabolizing enzymes. This may be the endogenous corticosteroid secreted as part of the stress response or exogenous steroid given to treat a disease.

Thyroid disease also changes the response to drugs [44]. Several mechanisms are involved. If patients are hyperthyroid then their heightened mental state will make them resistant to sedatives and analgesic drugs among others. In addition, some test substrates have a reduced half-life because of induced enzymes. Indeed, in some patients the hepatic endoplasmic reticulum has been seen to be hypertrophied on microscopy. Despite these changes there are few reports of changes in drug elimination caused by changes in the drug metabolizing enzymes. However, there are changes in the elimination of drugs in hyperthyroidism caused by changes in the amount and composition of plasma proteins. The most important drug affected by this is warfarin, although others may be similarly affected.

Hypothyroidism produces other changes. There is a 40% reduction in the oxidation of antipyrine, although it is unknown if this also occurs with drugs. Like hyperthyroidism, hypothyroidism changes the elimination of drugs through mechanisms other than changes in enzymes. Renal function is also reduced and this can itself cause an important reduction in the excretion of digoxin and practolol.

Many other hormones are affected by severe illness. Growth hormone is one of these. Its importance in the critically ill is now being recognized. Furthermore, it is a key regulator of the expression of many enzymes [98]. Its secretion is also different between men and women and explains the different expression of the most important drug metabolizing enzymes between the sexes. Other reasons for sex differences in the metabolism of drugs include using the oral contraceptive pill. This leads to a 49% increase in the clearance of paracetamol by inducing both glucuronidation and oxidation [148].

Changes in growth hormone secretion have also been implicated to explain the different effects on drug metabolism caused by morphine, but not by pethidine. Rane and colleagues [66] showed that morphine inhibits its own desmethylation, but not glucuronidation. In a subsequent study [122] they compared rats treated with morphine and pethidine. Morphine suppressed CYP 2C, CYP 3A and CYP 4A and induced CYP 1A2, CYP 2B1 and CYP 2E1. Both the enzyme itself and the mRNA were affected showing that the change occurred at the transcription level. Pethidine caused none of these changes.

The authors also used a variety of control animals exposed to several blocking agents. From this, and the similarity of the changes to other work, they concluded that this was a neuroendocrine effect resulting in a change in growth hormone that then altered the expression of the enzymes. The opioid receptors were not causing them, because pethidine caused no change. It is noteworthy that morphine (but not pethidine) occurs naturally in the brains of mammals [155].

The importance of this work in humans has been investigated. However, drugs such as codeine that depend on metabolism to morphine, may be less effective if morphine is given first.

AGE

The very old and the very young are treated in intensive care units. With both extremes of age significant differences in drug metabolism from the normal population exist. Both metabolism and excretion are affected.

Metabolic activity also varies with age. Phase I enzymes have been shown to change with age in animals [70]. The phase II enzymes responsible for the glucuronidation of morphine also change with age. Morphine is metabolized mostly to morphine-3-glucuronide (M-3G) and morphine-6-glucuronide (M-6G) by two different UDP glucuronyl transferases. In premature infants, Choonara and colleagues [30] showed that the clearance of morphine was decreased compared with children. However, they also noted that the M-3G:morphine ratio in plasma and urine and the M-6G:morphine ratio in urine were higher in children than in neonates. This indicates that there is enhancement of glucuronidation pathways with growth. Since there was no difference in the M-3G:M-6G ratio between children and neonates they also suggested that both glucuronidation pathways develop in a similar fashion.

Table 8 Effects of ageing in humans on various pharmacokinetic variables of drugs metabolized by cytochromes P450 (from [129])

Drug	Age (years)	Plasma half-life ($T_{\frac{1}{2}}$) (h)	Plasma clearance (ml kg^{-1} h)
Aminopyrine	25–30	3	
	65–85	10	
Antipyrine	20–40	12.5	
	65–92	16.8	
Phenobarbitone	20–40	71	
	50–60	77	
	70	107	
Phenytoin	20–43		26
	67–95		42

The elderly (> 65 yr) population is increasing. In the USA in 1980 it made up 11% of the population and is estimated to make up 15% by the year 2040 [60]. Many changes affect the elimination of many drugs in the elderly. These include a decreased body weight, body water, cardiac output, plasma concentration of albumin and an increased body fat. These changes have been well illustrated with midazolam [63]. However, Jacobs and colleagues [73] have also shown a pharmacodynamic sensitivity related to age independent of pharmacokinetic variables. There are significant changes in the elderly in the plasma half-life and clearance of drugs metabolized by cytochromes P450 (table 8).

The exact mechanisms behind these changes in enzymes are unknown. Work in rats has shown significant decreases in the activities of these enzymes with age. In addition, some studies have shown a decrease in rate of induction of these enzymes while others have not [129].

OTHER DRUGS

Many drugs will change the activity of both phase I and phase II systems. This may change the pattern of metabolites made from other drugs by these enzymes. For example M-3G and M-6G are made by different UDP-glucuronyl transferases. Phenobarbitone induces these different enzymes by varying amounts. When the metabolism of morphine was studied in liver microsomes from rats with and without pre-treatment with phenobarbitone the ratio of M-3G:M-6G varied [121]. The glucuronidation of morphine can also be inhibited by a variety of drugs, including oxazepam and salicylamide [112].

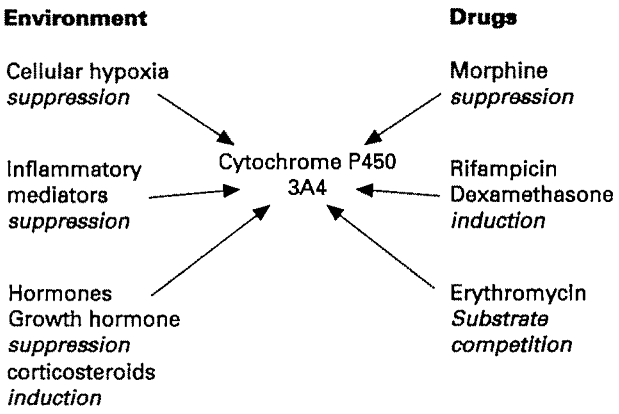

Figure 5 Some of the known factors affecting one enzyme, cytochrome P450 3A, showing how difficult it is to predict its function.

RENAL FAILURE

There is evidence that renal failure is associated with impaired drug metabolism [42] both in an experimental model [44], and in humans [124]. In rats, there is a decrease in hepatic cytochromes P450 after sub-total bilateral nephrectomy of sufficient degree to result in an increase in urea and creatinine [44]. It is also likely that the effect of renal failure on drug metabolism will also vary for different drugs. For example, propranolol, a drug thought to be exclusively cleared by the liver, is eliminated poorly in renal failure [17]. Conversely, the elimination of phenytoin is accelerated in uraemic patients [108].

INTERACTION OF FACTORS

Many factors will simultaneously change enzyme function in the critically ill. Figure 5 illustrates some of the factors that may affect one enzyme. How they interact with each other is unknown.

Metabolites

Morphine is metabolized principally by phase II enzymes to morphine-3 glucuronide (M-3G) and morphine-6 glucuronide (M-6G). Since these are both excreted in the urine, these metabolites will accumulate in renal failure. In 1986 we [133] and others showed that this metabolite accumulates in renal failure causing unexpected and prolonged narcosis in humans [110]. M-6G has been shown to be a potent analgesic and M-3G to antagonize this [56, 140]. It is noteworthy that some patients are unable to make M-6G and obtain poor analgesia from morphine. This suggests that analgesia depends upon the balance of the two metabolites that are produced.

Interestingly, both M-3G and M-6G are highly polar substances and therefore should not cross lipid membranes and so be active. A Swiss group [24] has shown that these two molecules behave as a molecular "chameleon". Both are able to change their configuration according to the environment they are in. When they are in a lipid environment they are fat soluble and in aqueous environment are water soluble.

More recently, one of the glucuronide metabolites of midazolam has also been shown to be active in humans. However, unlike the glucuronides of morphine that are many times more potent than the parent compound midazolam, 1-hydroxy glucuronide has only a tenth of the activity of the parent drug [10]. No molecular modelling has been done with this substance to see it if changes its configuration like morphine.

Other drugs also have active metabolites. These are summarized in table 9.

Extrahepatic sites of drug metabolism

The enzymes that metabolize drugs are found in most cells in the body. It is therefore not surprising that there is extrahepatic metabolism of many drugs [58, 59, 84, 114]. The amount of extrahepatic drug metabolism will vary greatly. In one of our studies with the new opioid, remifentanil, we found normal metabolism during the anhepatic period of liver transplantation [105] while morphine had very little metabolism [20]. This is because the enzymes metabolizing remifentanil are found in blood and other tissues while those metabolizing morphine are concentrated in the liver.

Many organs have been shown both *in vitro* and *in vivo* to metabolize drugs. Not surprisingly, the gut is an active metabolic organ since it is the body's first line of defence when dealing with many xenobiotics, including food! The brush border is the most active. When Kolars and colleagues [84] instilled cyclosporin, through a nasogastric tube, into the small bowel of anhepatic patients they were able to show

Table 9 Important metabolites of sedative and analgesic drugs. (Reproduced from [116])

Parent drug	Metabolite	Comments
Diazepam	Nordesmethyl diazepam, oxazepam	Both of these are active. They have a longer elimination half-life than diazepam. The elimination half-life of nordesmethyl diazepam can increase to 403 h
Midazolam	1-hydroxy midazolam	10 % of the activity of the parent drug
Midazolam	1-hydroxy midazolam glucuronide	Accumulates in renal failure and has $\frac{1}{10}$ the activity of midazolam
Morphine	Morphine-β-glucuronide	Antianalgesic
	Morphine-6-glucuronide	Potent analgesic properties, up to 40 times more active than parent drug when given intracisternly. Longer duration of action than morphine. Will be retained in renal failure
Vecuronium	Nordesacetyl vecuronium	Activity enhanced by hypomagnesaemia
Pethidine	Norphethidine	Can cause fits

significant amounts of metabolites in the portal blood. The gut also contains large amounts of bacteria that also have drug metabolizing enzymes. These bacteria have been shown to metabolize halothane [49].

Several authors [142, 153] have used slices of various organs, not just the intestines, and shown them to play an important part in extrahepatic drug metabolism. For example, many drug metabolizing enzymes are found in the renal cortex [2].

The lung has also been suggested as a site for drug metabolism. Cassidy and Houston [25, 26] have suggested that it may be an important site for phenol metabolism. However, when we studied the metabolism of propofol [59] and remifentanil [36] we could not show any metabolism by the lung.

How important these sites become in critical illness is unknown. There is only one case report of a viraemic patient having a liver transplant and having his extrahepatic sites of drug metabolism assessed by measuring the breakdown of midazolam. In this patient the extrahepatic enzymes appeared to be affected in the same way as enzymes in the liver [114].

The kidneys may also be affected by disease that changes drug metabolism. In patients with unilateral hydro-nephrosis the diseased kidney has less cytochrome P450 activity than the normal side [160]. Other diseases affecting the cortex may have similar effects [54].

Unexpected effects

Although clinicians recognize the effects of the drug on the primary organ unexpected effects can sometimes occur elsewhere in the body. These must be looked for otherwise the effects they cause may be attributed to the underlying disease.

PROPOFOL AND CYTOCHROMES P450

Propofol has achieved popularity as a sedative agent in the critically ill. It is given over many days and this results in a total dose many times larger than is used during anaesthesia being given. Because of this, insignificant effects during anaesthesia may become important in the critically ill. One potential interaction is between propofol and cytochromes P450.

One group in Iowa [8] showed that propofol is a specific inhibitor of rat cytochromes P450. They used microsomes from rats which had been treated with phenobarbitone and isoniazid inducing CYP 2B1, CYP 2C6 and CYP 3A and CYP 2E1. They showed inhibition of CYPs 2B1 and CYP 2C6 but could not show any significant inhibition of CYP 2E1. Another group using microsomes from pig and human liver showed that concentrations of propofol encountered in clinical practice inhibited the oxidative metabolism of sufentanil and alfentanil [74]. We have similarly shown inhibition of midazolam by propofol [unpublished observation].

Mouton-Perry and colleagues [103] have shown that the inhibitory effects of propofol occur in whole animals. They gave dogs propofol and measured the clearance of propranolol. Control animals were give soyabean extract (the solvent for propofol). Propofol caused a 40% decrease in the clearance of propranolol. Several mechanisms for this have been suggested. Interference with some part of the cytochrome P450 responsible for binding the drug has been suggested [8]. More recently, a group from Taipei [28] has shown in microsomes from hamsters, that propofol may bind to the main part of the haem ring in the cytochrome inactivating it. The haem part of the cytochrome is responsible for the addition of oxygen in the same way as haemoglobin. It is noteworthy that in contrast with the work in dogs, they could not reproduce this inhibitory effect in hamsters anaesthetized with propofol and given a variety of probe substrates. The importance of this in humans remains to be elucidated, although it may explain some of the changes seen in a recent study looking at the pharmacokinetics of propofol and alfentanil used together [47].

Deliberate enzyme inhibition

Enzyme inhibition is not always detrimental. The use of the enzyme inhibitor, cilastatin, with the antibiotic imipenem illustrates this. Imipenem is an antibiotic belonging to the carbopenem class of β lactams. It is broken down by the enzyme dehydropeptidase-1, found in brush border microvilli of the proximal tubule. The breakdown of imipenem prevents antibacterial concentrations of imipenem reaching distal parts of the kidney [22]. In urinary tract infections this is a major disadvantage. Dehydropeptidase-1 can be inhibited with cilastatin overcoming this and improving the efficacy of imipenem. Imipenem is marketed as a 1:1 mixture of antibiotic and enzyme inhibitor.

Interestingly cilastatin appears to be not only an enzyme inhibitor it also acts to prevent nephrotoxicity of high dose imipenem in rabbits [18] and cyclosporin in patients after heart transplantation [94]. Various mechanisms have been suggested for this, including changes in blood flow, reduction in tubular uptake of some molecules preventing toxic accumulation or decreasing cellular peptide turnover because of inhibition of the enzyme, but none has been proved [94].

Some volatile anaesthetics, especially halothane, are metabolized to hepatoxic metabolites, usually by CYP 2E1. This enzyme is inhibited by volatile anaesthetic agents and also by disulfiram. In future, inhibition of this enzyme may be used to reduce the toxicity of these drugs [57, 81].

Transport

Once the drug is in the blood it then needs to be transported to the receptor or other site of action and to the organs of elimination. Although there is a lot more information about transport within the blood, little is known about transport from the blood to the enzyme receptor. However, since transport may affect drug metabolism, by altering the amount presented to the enzyme, it is briefly discussed in this review.

There are many proteins in the blood—two are of major importance for carrying drugs. The first,

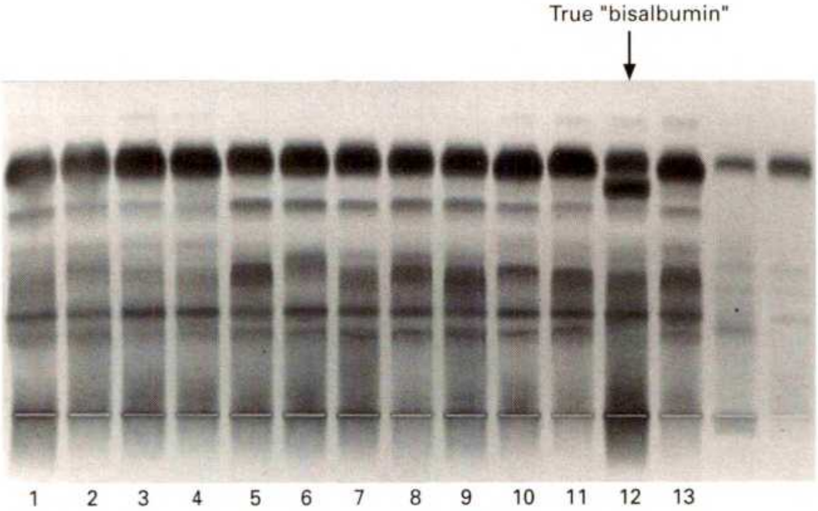

Figure 6 Electrophoretic strip showing true "bisalbumin" in lane 12.

Table 10 Changes in binding of drugs to plasma proteins in patients with renal failure. (From [42])

Drug	Change in binding
Acidic drugs:	
Desmethyldiazepam	Decreased [107]
Phenytoin	Decreased [3, 68, 109]
Benzylpenicillin	Decreased [43]
Salicylate	Decreased [3, 43]
Frusemide	Decreased [4, 123]
Warfarin	Decreased [7, 16]
Basic drugs:	
Disopyramide	Increased [65]
Vancomycin	Decreased [146]
Thiopentone	Decreased [3, 61]
Morphine	Decreased [109]

albumin, carries acidic drugs such as phenytoin and lignocaine. The other, alpha 1 acid glycoprotein, carries basic drugs such as morphine.

Drugs vary in the amount of their protein binding. Some drugs are not highly protein bound whereas others, such as warfarin and diazepam, are highly protein bound. In those drugs with a high protein binding displacement of even a small amount of drug will greatly increase the free or active drug. Thus, with warfarin, which is 99% bound to albumin, displacement of 1% of the boundary drug will double the active amount of drug. However, this increase in free fraction will also result in an increased extraction of the drug by the liver and changes in volume of distribution, reducing this effect [3, 127].

ALBUMIN

Albumin carries many drugs and other endo- and xenobiotics. The importance of albumin for drug transport and many other functions is being questioned. Plasma concentrations of albumin decrease in severe illness and maintaining "normal" plasma concentrations by giving albumin preparations has no effect on outcome [46, 55, 62, 141, 143, 144].

There are probably several reasons for this. Not surprisingly, for a protein with a molecular weight of about 65 000, there are several genetically acquired variants of albumin. These include albumin Reading, Chent, and Makie [95] as well as fast (albumin Naskapi) and slow (albumin Mexico); the last two

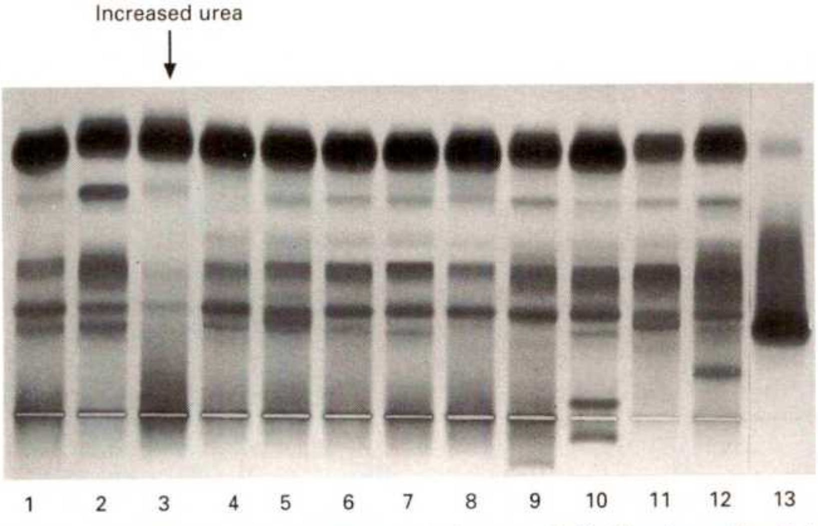

Figure 7 Electrophoresis of albumin. Lane 3 shows albumin from a critically ill patient with a high plasma concentration of urea. The front edge is "faster" than adjacent lanes.

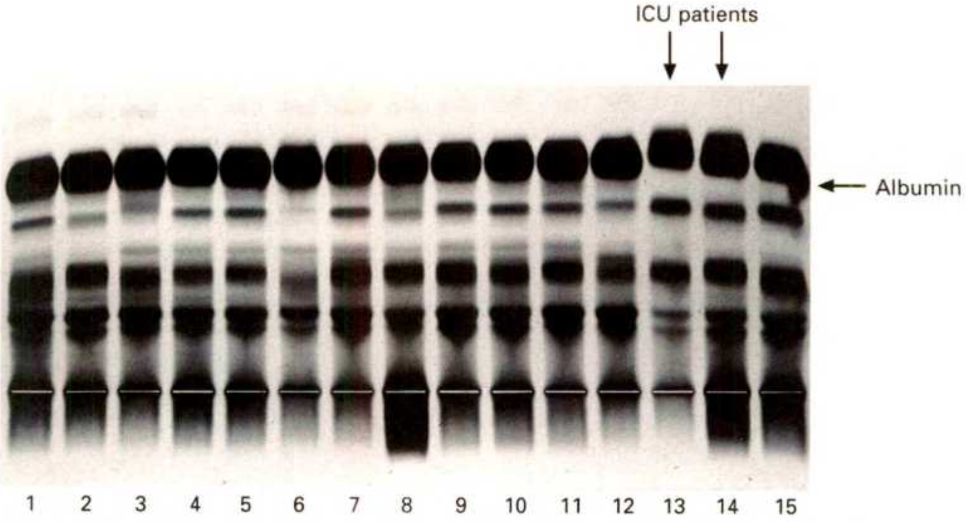

Figure 8 Electrophoresis of albumin from critically ill patients (lanes 13 and 14), other patients and control (lane 15). The albumin from the critically ill patients migrates faster than the others.

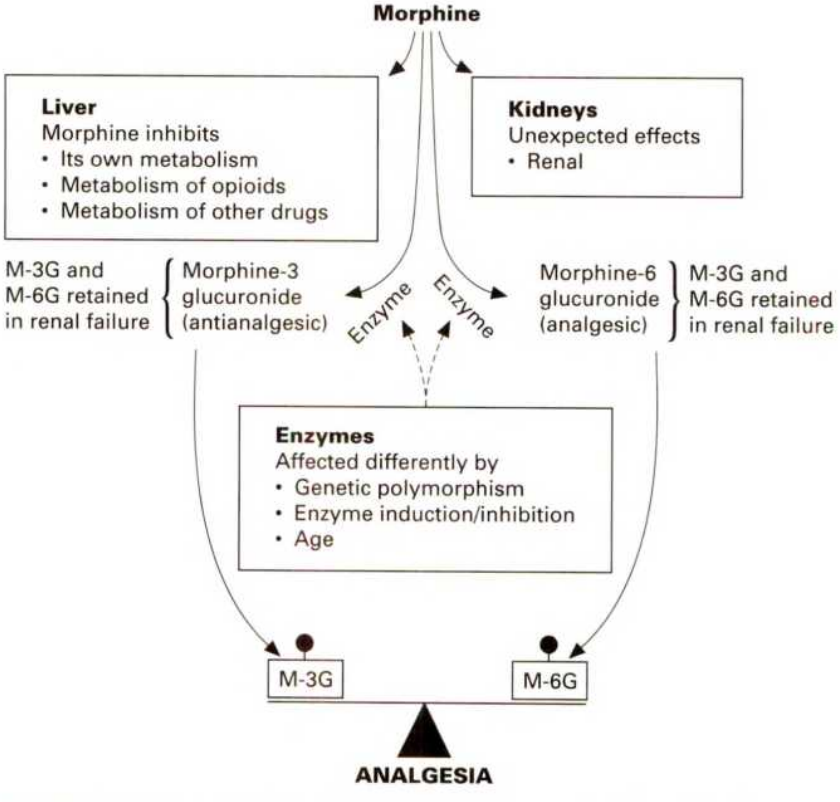
Morphine
Liver
Morphine inhibits
• Its own metabolism
• Metabolism of opioids
• Metabolism of other drugs
Kidneys
Unexpected effects
• Renal
M-3G and M-6G retained in renal failure
Morphine-3 glucuronide (antianalgesic)
Enzyme
Enzyme
Morphine-6 glucuronide (analgesic)
M-3G and M-6G retained in renal failure
Enzymes
Affected differently by
• Genetic polymorphism
• Enzyme induction/inhibition
• Age
M-3G
M-6G
ANALGESIA

Figure 9 How understanding the metabolism of morphine explains *some* of its unpredictability.

refer to electrophoretic mobility. An example of this is shown in figure 6. Lane 12 has a "double head" to it showing it to be hereditary, bisalbuminaemia.

Furthermore, the configuration of albumin also changes during illness. For example, in renal failure the binding of drugs to proteins may be increased or decreased (table 10).

The mechanism for the change in the configuration of albumin has been described for pancreatitis. Kobayashi and colleagues [83] have shown that pancreatic enzymes may cause bisalbumin to appear. Similarly, high dose antibiotics, urea or bilirubin may also cause this [83, 90]. The effects of urea on the electrophoretic pattern of albumin are shown in figure 7.

We have recently confirmed that this change in the electrophoretic characteristic occurs in the critically ill. Figure 8 shows a control lane (15) and next to it albumin from two critically ill patients. The remainder of the figure consists of outpatients and inpatients from the general wards. The two critically ill patients have albumin that electrophoreses more quickly than the others. Both the cause of the change and its significance are unknown, but it does show that albumin is not an inert molecule and changes with disease.

More recently, there is increasing awareness that the configuration of albumin found in pharmaceutical preparations is different from the configuration of albumin in the blood. Finally, there are some normal humans who do not make albumin at all, although studies on drug transport mechanisms have not been carried out. However, in analbuminaemic rats thyroxine (normally bound to albumin) transport is normal. [95]

The changes in albumin configuration in disease give strength to the belief of some that protein binding of drugs is not of such great importance as was previously thought, although others would contest this [126]. As albumin is expensive this is an area that is clearly in need of urgent investigation since one of the few arguments for supporting plasma albumin concentrations in the critically ill is to return drug carriage to normal. Infusing exogenous albumin may not achieve this.

ALPHA$_1$ ACID GLYCOPROTEIN

This protein increases after stress of many types, including surgery. It binds many drugs such as bupivacaine and so might be expected to reduce the free fraction of them [19]. However, this has not been shown and there are several reasons for this. Several different forms exist [130, 131] and these change with the severity and type of disease [93]. This may be related in some way to the inflammatory response [151]. Other changes also include an increase with age [157].

Application of our knowledge about drug metabolism

Understanding isolated changes in enzyme function unfortunately will not allow early prediction, at the moment, of how it will function in the critically ill. Some of the changes affecting one enzyme only are shown in figure 9. However, understanding these changes does mean that the unpredictability of drug metabolism becomes predictable—clinicians know what to look out for.

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References

1. Abdel-Razzak Z, Loyer P, Fautrel A, Gautier J, Corcos L, Turlin B, Beaune P, Guillouzo A. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. *Molecular Pharmacology* 1993; **44**: 707–715.
2. Anders MW. Metabolism of drugs by the kidneys. *Kidney International* 1980; **18**: 636–647.
3. Andreasen F. Protein binding of drugs in plasma from patients with acute renal failure. *Acta Pharmacologica et Toxicologica* 1973; **32**: 417–429.
4. Andreasen F, Jakobsen P. Determination of frusemide in blood plasma and its binding to proteins in normal plasma and plasma from patients with acute renal failure. *Acta Pharmacologica et Toxicologica* 1974; 32; 417–429.
5. Angus P, Morgan D, Smallwood R. Hypoxia and hepatic drug metabolism—clinical implications. *Alimentary Pharmacology Therapy* 1990; **4**: 213–225.
6. Armstrong SG, Renton KW. Mechanism of hepatic cytochrome P450 modulation during *Listeria monocytogenes* infection in mice. *Molecular Pharmacology* 1993; **43**: 542–547.
7. Bachmann K, Shapiro R, Mackiewivcz J. Influence of renal dysfunction on warfarin plasma protein binding. *Journal of Clinical Pharmacology* 1976; **16**: 168–172.
8. Baker MT, Chadam MV, Ronnenberg WC. Inhibitory effects of propofol on cytochrome P450 activities in rat hepatic microsomes. *Anesthesia and Analgesia* 1993; **76**: 817–821.
9. Barry M, Feely J. Enzyme induction and inhibition. *Pharmacology and Therapeutics* 1990; **48**: 71–94.
10. Bauer TM, Ritz R, Haberthur C, Ha HR, Hunkeler W, Sleight AJ, Scollo-Lavizzari G, Haefeli WE. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; **364**: 145–147.
11. Bayliss MK, Bell JA, Wilson K, Park GR. 7-Ethoxycoumarin O-deethylase kinetics in isolated rat, dog and human hepatocyte suspension. *Xenobiotica* 1994; **24**: 231–241.
12. Bechtel YC, Joanne C, Grandmottet M, Betchel PR. The influence of insulin-dependent diabetes on the metabolism of caffeine and the expression of the debrisouin oxidation phenotype. *Clinical Pharmacology and Therapeutics* 1988; **44**: 408–417.
13. Beck F, Whitehouse M. Impaired drug metabolism in rats associated with acute inflammation: A possible assay for anti-injury agents. *Proceedings of the Society for Experimental Biology and Medicine* 1974; **145**: 135–140.
14. Becker GL. Effects of nonvolatile agents on oxygen demand and energy status in isolated hepatocytes. *Anesthesia and Analgesia* 1988; **67**: 923–928.
15. Becker GL, Miletich DJ, Albrecht RF. Halogenated anesthetics increase oxygen consumption in isolated hepatocytes from phenobarbital-treated rats. *Anesthesiology* 1987; **67**: 185–190.
16. Belpaire FM, Bogaert MG, Mussche MM. Influence of renal failure on the protein binding of drugs in animals and man. *European Journal of Clinical Pharmacology* 1977; **11**: 27–32.
17. Bianchetti G, Graziani G, Branicaccio D. Pharmacokinetics and effects of propanolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clinical Pharmacokinetics* 1976; **1**: 373–384.
18. Birnbaum J, Kahan FM, Kropp H. Carbapenems, a new class of beta lactam antibiotics. Discovery and development of imipenem/cilastatin. *American Journal of Medicine* 1985; **78**: 3–21.
19. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *British Journal of Anaesthesia* 1990; **64**: 436–441.
20. Bodenham A, Quinn K, Park GR. Extra-hepatic metabolism of morphine. *British Journal of Anaesthesia* 1989; **63**: 380–384.
21. Bone RC, Balk RA, Cerra FB, Fein AM, Knaus WA, Schein RMH, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use on innovative therapies in sepsis. *Chest* 1992; **101**: 1644–1655.
22. Buckley MM, Brogden RN, Barradell LB, Goa KL. Imipenem/cilastatin. *Drugs* 1992; **44**: 408–444.
23. Burgess P, Hall RI, Bateman DN, Johnston IDA. The effect of total parenteral nutrition on hepatic drug oxidation. *Journal of Parenteral and Enteral Nutrition* 1987; **11**: 540–543.
24. Carrupt PA, Testa B, Bechalany A, El Tayar N, Descas P, Perrissoud D. Morphine 6-glucuronide and morphine 3-glucuronide as molecular chameleons with unexpected lipophilicity. *Journal of Medicinal Chemistry* 1991; **34**: 1272–1275.

25. Cassidy KM, Houston JB. In vivo capacity of hepatic and extrahepatic enzymes to conjugate phenol. *Drug Metabolism and Disposition* 1984; **12**: 619–624.
26. Cassidy MK, Houston JB. In vivo assessment of extrahepatic conjugative metabolism in first pass effects using the model compound phenol. *Journal of Pharmacy and Pharmacology* 1980; **32**: 57–59.
27. Chang KC, Laner BA, Bell JD, Chai H. Altered theophylline pharmacokinetics during acute respiratory viral illness. *Lancet* 1978; **1**: 1132–1133.
28. Chen TL, Ueng TH, Chen SH, Lee PH, Fan SZ, and Liu CC. Human cytochrome P450 mono-oxygenase system is suppressed by propofol. *British Journal of Anaesthesia* 1995; **74**: 558–562.
29. Cholerton S, Daly AK, Idle JR. The role of individual human cytochromes P450 in drug metabolism and clinical response. *TIPPS* 1992; **13**: 434–439.
30. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. *British Journal of Clinical Pharmacology* 1989; **28**: 599–604.
31. Craig PI, Mehta I, Murray M, McDonald D, Astrom A, van der Meide PH, Farrell G. Interferon down regulates the male-specific cytochrome P450IIIA2 in rat liver. *Molecular Pharmacology* 1990; **38**: 313–318.
32. Craig PI, Williams SJ, Cantrill E, Farrell GC. Rat but not human interferons suppress hepatic oxidative drug metabolism in rats. *Gastroenterology* 1989; **97**: 999–1004.
33. Craig RK. *Methods in molecular medicine.* 2nd ed. London: BMJ, 1993: 8–16.
34. de Waziers I, Garlatti M, Bouget J, Beaune PH, and Barouki R. Insulin down-regulates cytochrome P450 2B and 2E at the pretranscriptional level in the rat hepatome cell line. *Molecular Pharmacology* 1995; **47**: 474–479.
35. Du Souich P, Corteau H, Kobusch AB, Dalkara S, Ong H. Effect of hypoxia on the cytochrome P450 and theophylline metabolism. *European Journal of Pharmacology* 1990; **183**: 2122–2123.
36. Duthie DR, Muir KT, Baddoo HHK, Doyle AR, Stevens JJWM, Kirkham AJT, Gupta SK, Archer S, Navapurkar VU, Park GR. Remifentanil is not metabolised by the lung. *Anesthesiology* 1995; **83**: A324.
37. Egawa K, Yoshida M, Kasai N. An endotoxin-induced serum factor that depresses hepatic d-aminolevulinic acid synthetase activity and cytochrome P-450 levels in mice. *Microbiology Immunology* 1981; **25**: 1091–1096.
38. El Azhary R, Renton K, Mannering G. Effect of interferon inducing agents (Polyriboinosinic Acid. Polyribocytidylic Acid and Tilorone) on the heme turnover of hepatic cytochrome P450. *Molecular Pharmacology* 1980; **17**: 395–399
39. Elin R, Vesell E, Wolff S. Effects of etiocholanolone induced fever on plasma antipyrine half lives and the metabolic clearance. *Clinical Pharmacology and Therapeutics* 1975; **17**: 447–457.
40. Elliott SL, Morgan DJ, Angus PW, Ghabrial H, Smallwood RA. The effect of hypoxia and acidosis on propranolol clearance in the isolated perfused rat liver preparation. *Biochemical Pharmacology* 1993; **45**: 763–765.
41. Elliott SL, Morgan DJ, Angus PW, Ghabrial H, Watson RGP, Smallwood RA. The effect of hypoxia on propranolol clearance during anterograde and retrograde flow in the isolated perfused rat liver preparation. *Biochemical Pharmacology* 1993; **45**: 573–578.
42. Elston A, Bayliss MK, Park GR. Effect of renal failure on drug metabolism by the liver. *British Journal of Anaesthesia* 1993; **71**: 282–290.
43. Farrel PC, Grib NL, Fry DL, Popovich RP, Broviac JW. Babb AL. A comparison of in vitro and in vivo solute-protein binding interactions in normal and uraemic individuals. *Transactions of the American Society of Artificial Internal Organs* 1972; **18**: 268–276.
44. Farrell GC. Drug metabolism in extrahepatic disease. *Pharmacology and Therapeutics* 1987; **35**: 375–404.
45. Ferrari L, Herber R, Batt AM, Siest G. Differential effects of human recombinant interleukin-1 beta and dexamethasone on hepatic drug-metabolizing enzymes in male and female rats. *Biochemical Pharmacology* 1993; **45**: 2269–2277.
46. Foley EF, Borlase BC, Dzik WH, Bistrain BR, Benotti PN. Albumin supplementation in the critically ill. *Archives of Surgery* 1990; **125**: 739–742.
47. Frenkel C, Schuttler J, Ihmsen H, Rommelsheim K. Pharmacokinetics and pharmacodynamics of propofol/alfentanil infusions for sedation in ICU patients. *Intensive Care Medicine* 1995; **21**: 981–988.
48. Gallenkamp H, Epping J, Fuchshoften-Rockel M, Heusler H, Richter E. Zytochrom P450-gehalt und arzneimittelmetabolismus der leber im shock *Verh Dtsch Ges In Med* 1982; **88**: 1093–1096.
49. Ghantous H, Lofberg B, Tjaive H, Danielsson BRG, Dencker L. Extrahepatic sites of metabolism of halothane in the rat. *Pharmacology and Toxicology* 1988; **62**: 135–141.
50. Ghezzi P, Saccardo B, Bianchi M. Induction of xanthine oxidase and heme oxygenase and depression of liver drug metabolism by interferon: A study with different recombinant interferons. *Journal of Interferon Research* 1986; **6**: 251–256.
51. Ghezzi P, Saccardo B, Villa P, Rossi V, Bianchi M, Dinarrelo CA. Role of interleukin-1 in the depression of liver drug metabolism by endotoxin. *Infection and Immunity* 1986; **54**: 837–840.
52. Gibson G, Skett P. *Introduction to drug metabolism.* London: Chapman and Hall, 1986.
53. Gibson PR, Dudley FJ. Ischemic hepatitis: clinical features, diagnosis and prognosis. *Australian and New Zealand Journal of Medicine* 1984; **14**: 822–825.
54. Gibson TP. Renal disease and drug metabolism. An overview. *American Journal of Kidney Diseases* 1986; **8**: 7–17.
55. Golub R, Sorrento JJ, Cantu R, Nierman DM, Moideen A, Stein HD. Efficacy of albumin supplementation in the surgical intensive care unit: A prospective, randomised study. *Critical Care Medicine* 1994; **22**: 613–619.
56. Gong QL, Hedner J, Bjorkman R, Hedner T. Morphine-3-glucuronide may functionally antagonize morphine-6-glucuronide induced antinociception and ventilatory depression in the rat. *Pain* 1992; **48**: 249–255.
57. Graham SG, Tateishi T, Guengerich FP, Wood AJJ, Wood M. Inhalational anesthetics inhibit CYP 2E1 activity specifically. *Anesthesiology* 1995; **83**: A342.
58. Gray P, Park GR. Plasma concentrations of dopexamine during the anhepatic period of liver transplantation. *British Journal of Clinical Pharmacology* 1993; **37**: 92.
59. Gray P, Park GR, Cockshott ID, Douglas ED, Shuker B, Simons PJ. Propofol metabolism in man during the anhepatic and reperfusion phases of liver transplantation. *Xenobiotica* 1992; **22**: 105–114.
60. Greenblatt DJ, Sellers EM, Shader RI. Drug deposition in old age. *New England Journal of Medicine* 1982; **206**: 1081–1088.
61. Groneim MM, Pandya H. Plasma protein binding of thiopental in patients with impaired renal or hepatic function. *Anesthesiology* 1975; **42**: 545–549.
62. Grootendorst AF, van Wilgenburg MGM, de Laat PHJM, van der Hoven B. Albumin abuse in intensive care medicine. *Intensive Care Medicine* 1988; **14**: 554–557.
63. Harper KW, Collier PS, Dundee JW, Elliott P, Halliday NJ, Lowry KG. Age and nature of operation influence the pharmacokinetics of midazolam. *British Journal of Anaesthesia* 1985; **57**: 866–871.
64. Harris H, Whittaker M. Differential inhibition of human serum cholinesterase with fluoride: Recognition of two new phenotypes. *Nature* 1961; **191**: 496–498.
65. Haughey DB, Kraft CJ, Matzke GR, Keane WF, Halstenson CE. Protein binding of disopyramide and elevated alpha 1 acid glycoprotein concentrations in serum obtained from dialysis patients and renal transplant recipients. *American Journal of Nephrology* 1985; **5**: 35–39.
66. Heizmann P, Von Alten R. Determination of midazolam and its a-hydroxymetabolite in plasma by gas chromatography with electron capture detection. *High Resolution Chromatography* 1981; **4**: 266–269.
67. Hiller A, Olkkola KT, Isohanni P, Saarnivaara L. Unconsciousness associated with midazolam and erythromycin. *British Journal of Anaesthesia* 1990; **65**: 826–828.
68. Hooper WD, Bochner F, Eadie MJ. Plasma protein binding of diphenylhydantoin: effects of sex hormones, renal and

hepatic disease. *Clinical Pharmacology and Therapeutics* 1974; **15**: 276–282.

69. Idle J. Enigmatic variations. *Nature* 1988; **331**: 391–392.
70. Imaoka S, Fujita S, Funae Y. Age-dependent expression of cytochrome P-450s in rat liver. *Biochimica et Biophysica Acta* 1991; **1097**: 187–192.
71. Ismail S, Kokwaro GO, Back DJ, Edwards G. Effect of malaria infection on pharmacokinetics of paracetamol in rat. *Xenobiotica* 1994; **24**: 527–533.
72. Jacobs JR, Croughwell ND, Goodman DK, White WD, Reves JG. Effect of hypothermia and sampling site on blood esmolol concentrations. *Journal of Clinical Pharmacology* 1993; **33**: 360–365.
73. Jacobs JR, Reves JG, Marty J, White WD, Bai SA, Smith LR. Aging increases the pharmacodynamic sensitivity to the hypnotic effects of midazolam. *Anesthesia and Analgesia* 1995; **80**: 143–148.
74. Janicki PK, James MF, Erskine WA. Propofol inhibits enzymatic degradation of alfentanil and sufentanil by isolated liver microsomes in vitro. *British Journal of Anaesthesia* 1992; **68**: 311–312.
75. Johansson I, Lindros KO, Erikasson H, Ingelman-Sundberg M. Transcriptional control of CYP 2E1 in the perivenous liver region and during starvation. *Biochemistry Biophysical Research Communication* 1990; **173**: 331–338.
76. Jones DP, Mason HS. Gradients of O_2 concentration in hepatocytes. *Journal of Biological Chemistry* 1978; **253**: 4874–4880.
77. Kalow W, Genest K. A method for the detection of atypical forms of human serum cholinesterase: determination of dibucaine numbers. *Canadian Journal of Biochemistry* 1957; **35**: 339.
78. Kanazawa Y, Kitada M, Mori T. Ascorbic acid deficiency decreases specific forms of cytochrome P-450 in liver microsomes of guinea pigs. *Molecular Pharmacology* 1991; **39**: 456–460.
79. Kappas A, Anderson KE, Conney AH, Alvares AP. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clinical Pharmacology and Therapeutics* 1976; **20**: 643–653.
80. Kelly SD, Cauldwell CB, Fisher DM, Lau M, Sharma ML, Weisiger RA. Recovery of hepatic drug extraction after hypothermic preservation. *Anesthesiology* 1995; **82**: 251–258.
81. Kharasch ED, Hankins D, Mautz D, Thummel KE. Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. *Lancet* 1996; **347**: 1367–1371.
82. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification. *Critical Care Medicine* 1985; **13**: 818–829.
83. Kobayashi S, Okamura N, Kamoi K, Sugita O. Bisalbumin (fast and slow type) induced by human pancreatic juice. *Annals of Clinical Biochemistry* 1995; **32**: 63–67.
84. Kolars JC, Awni WM, Merion RM, Watkins PB. First-pass metabolism of cyclosporin by the gut. *Lancet* 1991; 1488–1489.
85. Kopf M, Baumann H, Freer G, Freudenberg M, Lamers M, Kishimoto T, Zinkernagel R, Bleuthmann H, Kohler G. Impaired immune and acute phase responses in interleukin-6-deficient mice. *Nature* 1994; **368**: 339–342.
86. Krishnaswamy K, Naidu AD. Microsomal enzymes in malnutrition as determined by plasma half-life of antipyrine. *British Medical Journal* 1977; **1**: 538–540.
87. Kronbach T, Mathys D, Umeno M, Gonzalez FJ, Meyer UA. Oxidation of midazolam and triazolam by human liver Cytochrome P450 IIIA4. *Molecular Pharmacology* 1989; **36**: 89–96.
88. Kurokohchi K, Yoneyama H, Matsuo Y, Nishioka M, Ichikawa Y. Effects of interleukin 1 alpha on the activities and gene expression of the cytochrome P450IID subfamily. *Biochemical Pharmacology* 1992; **44**: 1669–1674.
89. Lambert A, Mitchell R, Frost J, Ratcliffe JG, Robertson WR. Direct in vitro inhibition of adrenosteroidogenesis of etomidate. *Lancet* 1983; **2**: 1085–1086
90. Lapresle C, Wal J. The binding of penicillin to albumin molecules in bisalbuminemia induced by penicillin therapy. *Biochimica et Biophysica Acta* 1979; **586**: 106–111.
91. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; **1**: 1270.
92. Leemann T. Cles pur une prediction plus rationelle des interactions medicamenteuses. *Medicine et Hygiene* 1993; **51**: 1033–1038.
93. Mackiewicz A, Khan MA, Gorny A, Kapcinska M, Juszczyk J, Calabrese LH, Espinosa LR. Glycoforms of alpha1-acid glycoprotein in era of human immunodeficiency virus-infected patients. *Journal of Infectious Diseases* 1994; **169**: 1360–1363.
94. Markewitz A, Hammer C, Pfeiffer M, Zahn S, Dreschesel J, Reichenspurner H, Reihart B. Reduction of cyclosporin induced nephrotoxicity by cilastatin following clinical heart transplantation. *Transplantation* 1994; **57**: 865–870.
95. McKusick VA, Francomano CA, Antonarakis SE. *Autosomal Dominant Phenotypes*. 10th ed. Baltimore and London: Johns Hopkins University Press, 1991: 39–44.
96. Mehta MU, Venkataramanan R, Burckart GJ, Ptachcinski RJ, Yang SL, Gray JA, Van Thiel DH, Starzl TE. Antipyrine kinetics in liver disease and liver transplantation. *Clinical Pharmacology and Therapeutics* 1986; **39**: 372–377.
97. Miahin V, von Bahr C, Ingelman-Sundberg M. Chlormethiazole as a potent and selective inhibitor in vivo of CYP2E1 during food deprivation. *First International Conference on Food Nutrition and Chemical Toxicity Guildford England* 1991.
98. Mode A, Gustafsson J, Jansson J, Eden S, Isaksson O. Association between plasma level of growth hormone and sex differentiation of hepatic steroid metabolism in the rat. *Endocrinology* 1982; **111**: 1692–1696.
99. Moochhala SM. Alteration of drug biotransformation by interferon and host defense mechanism. *Annals Academy of Medicine* 1991; **20**: 13–18.
100. Moochhala S, Renton K. Effects of the interferon inducing agent, PolyrI.rC on the synthesis of hepatic cytochrome P450. *Asia Pacific Journal of Pharmacology* 1989; **4**: 83–88.
101. Morgan ET. Suppression of constitutive cytochrome P450 gene expression in livers of rats undergoing an acute phase response to endotoxin. *Molecular Pharmacology* 1989; **36**: 699–707.
102. Morgan ET, Norman CA. Pretranslational suppression of cytochrome P-450h (IIC11) gene expression in rat liver after administration of interferon inducers. *Drug Metabolism and Disposition* 1990; **18**: 649–653.
103. Mouton Perry S, Whelan E, Shay S, Wood AJJ, Wood M. Effect of i.v. anaesthesia with propofol on drug distribution and metabolism in the dog. *British Journal of Anaesthesia* 1991; **66**: 66–72.
104. Murray M. Metabolite intermediate complexation of microsomal cytochrome P450 2C11 in male rat liver by nortriptyline. *Molecular Pharmacology* 1992; **42**: 931–938.
105. Navapurkar V, Archer S, Gupta SK, Frazer N, Muir SK, Park GR. Pharmacokinetics of remifentanil during hepatic transplantation. *Anesthesiology* 1995; **83**: A382.
106. Nebert DW, Nelson DR, Coon MJ, Estabrook RW, Feyereisen R, Fuji-Kuriyama Y, Gonzalez FJ, Guengerich FP, Gunsalus IC, Johnson EF, Loper JC, Sato R, Waterman MR, Waxman DJ. The P450 superfamily: Update on new sequences, gene mapping, and recommended nomenclature. *DNA and Cell Biology* 1991; **10**: 1–14.
107. Ochs HR, Rauh HW, Greenblatt DJ, Kaschell HJ. Clorazepate disposition and diazepam in renal insufficiency: serum concentrations and proteins binding of diazepam and desmethyl diazepam. *Nephron* 1984; **37**: 100–104.
108. Odar-Cederlof I, Borga O. Kinetics of diphenylhydantoin in uremic patients: Consequences of decreased plasma protein binding. *European Journal of Clinical Pharmacology* 1974; **7**: 31–37.
109. Olson GD, Bennett WM, Porter GA. Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. *Clinical Pharmacology and Therapeutics* 1975; **17**: 677–684.
110. Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *British Medical Journal* 1986; **292**: 1548–1549
111. Ostengaard D, Jensen FS, Jensen E, Skovgaard LT, Viby-Mogensen J. Mivacurium-induced neuromuscular blockade

in patients with atypical plasma cholinesterase. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 314–318.

112. Pacifici GM, Rane A. Inhibition of morphine glucuronidation by oxazepam in human fetal liver microsomes. *Drug Metabolism and Disposition* 1981; **9**: 569–572.
113. Park GR, Larroque C, Maurel P. Serum from critically ill patients changes the metabolism of progesterone. *Anaesthesia* 1994; **49**: 347–348.
114. Park GR, Manara AR, Dawling S. Extrahepatic metabolism of midazolam. *British Journal of Clinical Pharmacology* 1989; **27**: 634–637.
115. Park GR, Miller E, Navapurkar V. What changes drug metabolism in critically ill patients II? Serum interferes with midazolam metabolism. *Anaesthesia* 1996; (in press).
116. Park GR, Navapurkar VU, Koller J. Pharmacology of sedative and analgesic agents in the critically ill. In: Park GR, Sladen RN, eds. Oxford: Blackwell Science, 1995; **2**: 18–50.
117. Park GR, Pichard L, Tinel M, Larroque C, Elston A, Domerque J, Dexionne B, Maurel P. What changes drug metabolism in critically ill patients? Two preliminary studies in isolated hepatocytes. *Anaesthesia* 1994; **49**: 188–191.
118. Peterson TC, Renton KW. The role of lymphocytes, macrophages and interferon in the depression of drug metabolism by dextran sulphate. *Immunopharmacology* 1986; **11**: 21–28.
119. Pineau T, Daujat M, Pichard L, Giraud F, Angevain J, Bonfils C, Maurel P. Developmental expression of rabbit cytochrome P450 CYP1A1, CYP1A2 and CYP3A6 genes. Effect of weaning and rifampacin. *European Journal of Biochemistry* 1991; **197**: 145–153.
120. Pollack GM, Browne JL, Marton J, Haberer LJ. Chronic stress impairs oxidative metabolism and hepatic excretion of model xenobiotic substrates in the rat. *Drug Metabolism and Disposition* 1991; **19**: 130–134.
121. Rane A, Gawronska-Szklarz B, Svensson J. Natural(−)- and unnatural(+)-enantiomers of morphine: Comparative metabolism and effect of morphine and phenobarbital treatment. *Journal of Pharmacology and Experimental Therapeutics* 1985; **234**: 761–765.
122. Rane A, Liu Z, Henderson CJ, and Wolf CR. Divergent regulation of cytochrome P450 enzymes by morphine and pethidine: a neuroendocrine mechanism? *Molecular Pharmacology* 1995; **47**: 57–64.
123. Rane A, Villeneuve JP, Stone WJ, Nies AS, Wilkinson GR, Branch RA. Plasma binding and distribution of frusemide in nephrotic syndrome and in uraemia. *Clinical Pharmacology and Therapeutics* 1978; **24**: 199–207.
124. Reidenberg MM. The biotransformations of drugs in renal failure. *American Journal of Medicine* 1977; **62**: 482–485.
125. Renton KW, Mannering GJ. Depression of hepatic cytochrome P-450 hepatic monoxygenase systems with administered interferon inducing agents. *Biochemistry Biophysical Research Communication* 1976; **73**: 343–348.
126. Reves JG, Newfield P, Smith LR. Midazolam induction time: association with serum albumin. *Anesthesiology* 1981; **55**: A259.
127. Rolan PE. Plasma protein binding displacement interactions—why are they still regarded as clinically important? *British Journal of Clinical Pharmacology* 1994; **37**: 125–128.
128. Schaefer CF, Biber B, Lerner MR, Jöbsis-VanderVliet FF, Fagraeus L. Rapid reduction of intestinal cytochrome *a*,*a*3 during lethal endotoxemia. *Journal of Surgical Research* 1991; **51**: 382–391.
129. Schumucker DL. Drug deposition in the elderly: a review of the critical factors. *Journal of the American Geriatrics Society* 1984; **32**: 144–149.
130. Serbource-Goguel N, Corbic M, Erlinger S, Durand G, Agnerey J, Feger J. Measurement of serum 1-acid glycoprotein and 1-antitrypsin desialylation in liver disease. *Hepatology* 1983; **3**: 356–359.
131. Serbource-Goguel N, Durand G, Corbic M, Agneray J, Feger J. Alterations in relative proportions of microheterogenous forms of human 1-acid glycoprotein in liver disease. *Journal of Hepatology* 1986; **2**: 245–252.
132. Shedlofsky SI, Swim AT, Robinson JM, Gallicchio VS, Cohen DA, McClain CJ. Interleukin-1 (IL1) depresses cytochrome P450 levels and activity in mice. *Life Sciences* 1987; **40**: 2331–2336.
133. Shelly MP, Cory EP, Park GR. Pharmacokinetics of morphine in two children before and after liver transplantation. *British Journal of Anaesthesia* 1986; **58**: 1218–1223.
134. Shelly MP, Dixon JS, Park GR. The pharmacokinetics of midazolam following orthotopic liver transplantation. *British Journal of Clinical Pharmacology* 1989; **27**: 629–633.
135. Shelly MP, Park GR, Mendel L. Failure of critically ill patients to metabolise midazolam. *Anaesthesia* 1987; **42**: 619–626.
136. Shelly MP, Quinn K, Park GR. Pharmacokinetics of morphine in patients following liver transplantation. *British Journal of Anaesthesia* 1989; **63**: 375–379.
137. Shelly MP, Walker S, Park GR. The pharmacokinetics of alfentanil in patients following liver transplantation. *Advances in the Biosciences* 1989; **76**: 643–646.
138. Shingu K, Eger EL, Johnson BH. Hypoxia per se can produce hepatic damage without death in rats. *Anesthesia and Analgesia* 1982; **61**: 820–823.
139. Shobha JC, Raghuram TC, Deva Kumar A, Krishnaswamy K. Antipyrine kinetics in undernourished diabetics. *European Journal of Clinical Pharmacology* 1991; **41**: 359–361.
140. Smith MT, Watt JA, Cramond T. Morphine-3-glucuronide a potent antagonist of morphine analgesia. *Life Science* 1990; **47**: 579–585.
141. Soni N. Wonderful albumin? *British Medical Journal* 1995; **310**: 887–888.
142. Stevenson IH, Dutton GJ. Glucuronide synthesis in kidney and gastrointestinal tract. *Biochemical Journal* 1962; **82**: 330–339.
143. Stockwell MA, Soni N, Riley B. Colloid solutions in the critically ill. A randomised comparison of albumin and polygeline. 1. Outcome and duration of stay in the intensive care unit. *Anaesthesia* 1992; **47**: 3–6.
144. Stockwell MA, Soni N, Riley B. Colloid solutions in the critically ill. A randomised comparison of albumin and polygeline. 2. Serum albumin concentration and incidences of pulmonary oedema and acute renal failure. *Anaesthesia* 1992; **47**: 7–9.
145. Sujita K, Okuno F, Tanaka Y, Hirano Y, Inamoto Y, Eto S, Arai M. Effect of interleukin 1 (IL-1) on the levels of cytochrome P-450 involving IL-1 receptor on the isolated hepatocytes of rat. *Biochemical & Biophysical Research Communications* 1990; **168**: 1217–1222.
146. Tan CC, Lee HS, Ti TY, Lee EJ. Pharmacokinetics of intravenous vancomycin in patients with end stage renal failure. *Therapeutic Drug Monitoring* 1990; **12**: 29–34.
147. Tarbit MH, Bayliss MK, Herriott D, Hood SR, Hutson JL, Park GR, Serabjit-Singh CJ. Applications of molecular biology and in vitro technology to drug metabolism studies: an industrial perspective. *Biochemical Society Transactions* 1993; **21**: 1018–1023.
148. Teunissen MWE, Srivastava AK, and Breimer DD. Influence of sex and the oral contraceptive steroids on antipyrine metabolite formation. *Clinical Pharmacology and Therapeutics* 1982; **32**: 240–246.
149. Trenholme G, Williams R, Rieckmann K, Frischer H, Carson P. Quinine disposition during malaria and during induced fever. *Clinical Pharmacology and Therapeutics* 1976; **19**: 459–467.
150. Tsutsumi M, Lasker JM, Shimizu M, Rosman AS, Lieber CS. The intralobular distribution of ethanol-inducible P450 IIEI in rat and human liver. *Hepatology* 1989; **10**: 437–446.
151. Vasson MP, Roch-Arveiller M, Couderc R, Baguet JC, Raichvarg D. Effects of alpha-1 acid glycoprotein on human polymorphonuclear neutrophils: influence of glycan microheterogeneity. *Clinica Chimica Acta* 1994; **224**: 65–71.
152. Venkataramanan R, Kalp K, Rabinovitch R, Cuellar R, Ptachcinski RJ, Teperman L, Makowka L, Burckart GJ, Van Thiel DH, Starzl TE. Conjugative drug metabolism in liver transplant patients. *Transplant Proceedings* 1989; **21**: 2455.
153. Vickers AE, Fischer V, Connors S, Fisher RL, Baldeck J, Maurer G, Brendel K. Cyclosporin A metabolism in human liver, kidney, and intestine slices. Comparison to rat and dog

slices and human cell lines. *Drug Metabolism and Disposition* 1992; **20**: 802–809.

154. Wang GL, Semenza GL. General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. *Proceedings of the National Academy of Sciences of the USA* 1993; **90**: 4304–4308.
155. Weitz CJ, Lowney LI, Faull KF, Feistner G. Goldstein A. Morphine and codeine from mammalian brain. *Neurobiology* 1986; **83**: 9784–9788.
156. Whittaker M, Britten JJ, Wicks RJ. Inhibition of the plasma cholinesterase variants by propranolol. *British Journal of Anaesthesia* 1981; **53**: 511–516.
157. Woo J, Chan HS, Or KH, Arumanayagam M. Effects of age and disease on two drug binding proteins: albumin and alpha-1-acid glycoprotein. *Clinical Biochemistry* 1994; **27**: 289–292.
158. Yang CS, Brady JF, Hong J. Dietary effects on cytochrome P450, xenobiotic metabolism and toxicity. *FASEB Journal* 1992; **6**: 737–744.
159. Yun Y, Casazza JP, Sohn DH, Veech RL, Song BJ. Pretranslational activation of cytochrome P450IIE during ketosis induced by a high fat diet. *Molecular Pharmacology* 1992; **41**: 474–479.
160. Zenser TV, Rapp NS, Mattammal MD. Renal cortical drug and xenobiotic metabolism following urinary tract obstruction. *Kidney International* 1984; **25**: 747–752.

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Determinants of splanchnic blood flow

J. TAKALA

The splanchnic region participates in the regulation of circulating blood volume and systemic blood pressure [60]. Major reduction of splanchnic blood volume and flow can be vital in defending the perfusion of the brain and the heart in acute hypovolaemia, but prolonged hypoperfusion of the splanchnic region will inevitably lead to hypoxic tissue injury [55]. The splanchnic region is also an important source and target of inflammatory mediators, which have a major impact on both systemic and regional blood flow and tissue functions [45]. The splanchnic circulation is in close interaction with the systemic haemodynamics under normal conditions. In the intensive care patient at risk of multiple organ failure, there is a complex and poorly understood interaction between the splanchnic blood flow, metabolic demands of the tissues and the mediators of inflammation and vasoregulation.

Inadequate splanchnic blood flow and tissue perfusion are likely to contribute to the development of organ failures and increased mortality in various categories of intensive care patients [8]. Monitoring of gastric intramucosal pH (pH_i) or intramucosal $P\text{CO}_2$ by gastrointestinal tonometry has provided an indicator of splanchnic tissue perfusion that is feasible for clinical use in intensive care [15, 18, 19, 27, 30, 32, 47, 48, 49]. Clinical studies using gastrointestinal tonometry have produced evidence to support the concept of a link between inadequate splanchnic tissue perfusion and multiple organ failure.

Gastric intramucosal acidosis, suggesting inadequate splanchnic tissue perfusion, is relatively common: up to 50% of patients admitted to intensive care with signs of circulatory failure, 50% of patients undergoing elective cardiac surgery and 18% of patients undergoing abdominal aortic surgery have at least transient episodes of gastric intramucosal acidosis [15, 18, 19, 30, 32, 47, 48, 49]. Patients with gastric intramucosal acidosis on admission to intensive care have an increased occurrence of multiple organ failure and increased mortality [30, 32, 47, 48]. Prevention and treatment of gastric intramucosal acidosis by administration of fluids and vasoactive drugs improves the outcome of those patients with normal pH_i on admission [32, 49].

The mechanisms responsible for the increased morbidity and mortality related to the inadequate splanchnic perfusion are far from being solved. Evidently alterations in systemic haemodynamics can impair the splanchnic blood flow and tissue perfusion [33, 55]. Tissue hypoxia with consequent direct hypoxic tissue injury, although likely to contribute, is clearly a too simplistic explanation. Translocation of bacteria and toxic substances, as a result of hypoxic intestinal mucosal injury, may occur but is unlikely to be a major factor [14]. Inadequate mucosal perfusion increases the intestinal mucosal permeability [20]. All these mechanisms and ischaemia and reperfusion of splanchnic tissues may contribute to the activation of inflammatory mediator networks, and thereby further modify the circulatory and metabolic responses locally, within the splanchnic region and in extrasplanchnic organs [46].

This review discusses the physiology of splanchnic blood flow, obtained largely from experimental studies, and the relatively limited available human data on splanchnic blood flow in patients at risk of multiple organ failure.

Splanchnic blood flow in normal conditions

The arterial inflow to the splanchnic region is via the coeliac trunk and the superior and inferior mesenteric arteries [17] (table 1). The venous efflux via the portal vein represents the sum of all splanchnic arterial influx, except the hepatic arterial flow. The venous efflux via the hepatic veins (i.e. the blood flow through the liver) represents the total hepatosplanchnic blood flow; in principle, the hepatic arterial flow could be estimated as the difference between portal venous flow and total hepatic venous efflux.

Hepatic arterial and portal venous blood flow interact closely. Owing to this "hydrodynamic" interaction, an alteration of flow to one of the circuits leads to an opposite change in the other circuit. The interaction tends to maintain total liver blood flow constant [57].

The blood flow of the small intestinal villus deserves special consideration. The artery and vein of the villus run in parallel but their blood flows are

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Key words

Blood, flow. Arteries. Oxygen, uptake. Gastrointestinal tract, blood flow.

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Table 1 Arterial blood supply to the splanchnic region (general overview, anatomical variation is common)

Main artery	Main tributary arteries	Main areas supplied
Coeliac trunk	Common hepatic (branches: right gastric and gastroduodenal)	Liver; parts of stomach, duodenum and pancreas
	Splenic	Spleen; parts of stomach and pancreas
	Left gastric	Parts of stomach and lower oesophagus
Superior mesenteric artery	Inferior pancreaticoduodenal, intestinal (12–15 branches), ileocolic, right colic, middle colic	Small intestine, caecum, ascending colon, most of transverse colon; parts of duodenum and pancreas
Inferior mesenteric artery	Left colic, sigmoid, superior rectal	Descending and sigmoid colon; parts of transverse colon and rectum

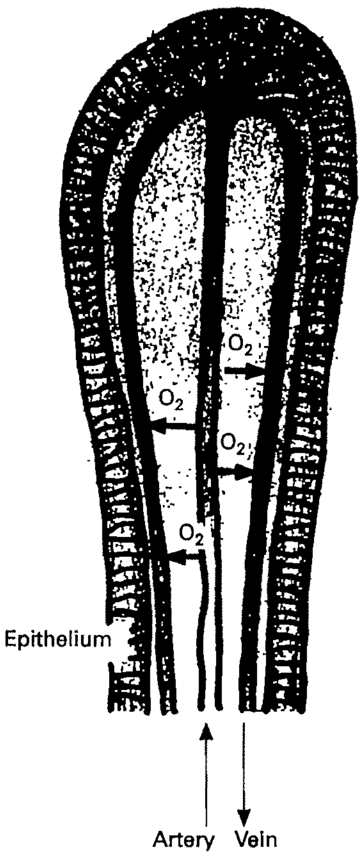

Figure 1 Schematic presentation of the intestinal villus countercurrent exchange of oxygen. Oxygen diffuses from the artery to the villous veins throughout their course to the tip of the villus. This results in a descending gradient of Po_2 from the base of the villus to the tip.

in opposite directions (fig. 1). The artery forms a dense capillary network close to the top of the villus. This anatomical arrangement allows countercurrent exchange of oxygen from the artery to the vein along their course within the villus [42]. This results in a descending gradient of tissue Po_2 from the base of the villus to its tip. This gradient is inversely related to the blood flow. An alternative explanation for the tissue Po_2 gradient in the villus may be a higher metabolic activity of the absorptive cells at the tip [42]. Regardless of the mechanism, the lower Po_2 at the tip may make the villus susceptible to tissue hypoxia, if vasoconstriction occurs for any reason.

Table 2 Splanchnic and whole body blood flow and oxygen uptake at rest [6, 24, 57, 77]

	Splanchnic	Whole body	Splanchnic contribution to total (%)
Blood flow (litre min^{-1} m^{-2})	0.50–0.80	2.5–4.0	20–30
Oxygen consumption (ml min^{-1} m^{2})	20–40	110–150	20–35
Oxygen extraction fraction	0.22–0.35	0.22–0.30	

MEASUREMENT OF SPLANCHNIC BLOOD FLOW

Human studies on splanchnic blood flow are relatively scarce owing to methodological difficulties of quantitative measurements. Direct measurement of splanchnic blood flow is practically impossible without surgery for anatomical reasons (table 1; multivessel influx and efflux, mixing of portal venous and hepatic arterial blood within the liver). The same is true for intravascular pressures within the splanchnic bed. Accordingly, much of the basic splanchnic circulatory physiology has been extrapolated from experimental studies and has not been confirmed in normal humans.

Total hepatosplanchnic blood flow can be estimated according to the Fick principle from the hepatic uptake of substances that are exclusive metabolized by the liver and distributed in the plasma [9, 36, 71]. Hepatic venous catheterization is necessary for the measurement. A detailed description of this technique and its evaluation both in normal subjects and in intensive care patients has been published [71].

SPLANCHNIC BLOOD FLOW AND OXYGEN UPTAKE

The splanchnic blood flow should be considered in relation to the splanchnic metabolic activity and the oxygen extraction capabilities of the splanchnic tissues. Normally, the total hepatosplanchnic blood flow is approximately 20–30 % of cardiac output. Roughly 80 % of the total hepatic blood flow reaches the liver via the portal vein and 20 % via the hepatic artery (a tributary of the coeliac trunk). The splanchnic oxygen consumption at rest is approximately 20–35 % of whole body oxygen consumption.

This results in a slightly increased oxygen extraction fraction, compared with the systemic oxygen extraction at rest [6, 24, 57, 77] (table 2).

When the metabolic demands of the splanchnic region increase, for example, as the result of feeding, blood flow to the relevant organs increases in proportion to the increase in regional oxygen consumption. Accordingly, the splanchnic oxygen extraction ratio is well maintained. If the oxygen extraction is very low, increased extraction may precede increases in blood flow. The appropriate increase in splanchnic perfusion can be obtained by either increased cardiac output or its redistribution, or by the combination of the two mechanisms [5, 23, 57, 67].

Probably because of its important role in the regulation of blood volume and redistribution of blood flow, the splanchnic region has a large capacity to adapt to reduced blood flow by increasing the oxygen extraction. During exercise, blood flow is redistributed from the splanchnic region to the working muscle [58, 59]. Splanchnic oxygen extraction increases consequently. At least in the short term, the normal metabolic processes are maintained at high levels of oxygen extraction. In extreme conditions, when hypoxia due to reduced inspired oxygen fraction is superimposed on exercise, splanchnic oxygen extraction may increase to close to 90%. During this acute experiment, hepatic extraction of indocyanine green decreased, suggesting that the liver function was deteriorating [58].

The available data in humans suggest that the liver is well protected against hypoxia in normal subjects, at least when the exposure is short. On the other hand, the gut may be more susceptible to develop local or regional hypoxia. Experimental studies suggest that the gut may become hypoxic already, when its oxygen extraction approaches 70% [50, 78].

CONTROL OF SPLANCHNIC BLOOD FLOW

Gut blood flow

Gut blood flow is regulated by intrinsic and extrinsic mechanisms. The intrinsic factors include local metabolic control and myogenic control, local reflexes and locally produced vasoactive substances. The extrinsic factors include sympathetic innervation, circulating vasoactive substances and systemic haemodynamic changes [23]. The total blood flow to the gut wall is unevenly distributed in the four main layers—the mucosa, the submucosa, the muscularis and the serosa. The mucosa and the submucosa receive most of the flow, up to 90%. Changes in the total gut blood flow may influence the flow to the different layers to varying extent.

The local metabolic control responds by local vasodilatation, if blood flow is insufficient for the local metabolic needs [23, 25]. The actual signal for the vasodilatation is not known. Both tissue Po_2 and products of cell metabolism have been proposed. The myogenic control responds to an increase in vascular transmural pressure by arteriolar vasoconstriction [23, 35]. These two control mechanisms interact to maintain blood flow adequate for metabolic needs, and to minimize changes in the intestinal capillary pressure and transcapillary fluid flux. Nitric oxide participates the vasoregulation of the hepato-splanchnic bed; its role is discussed separately later.

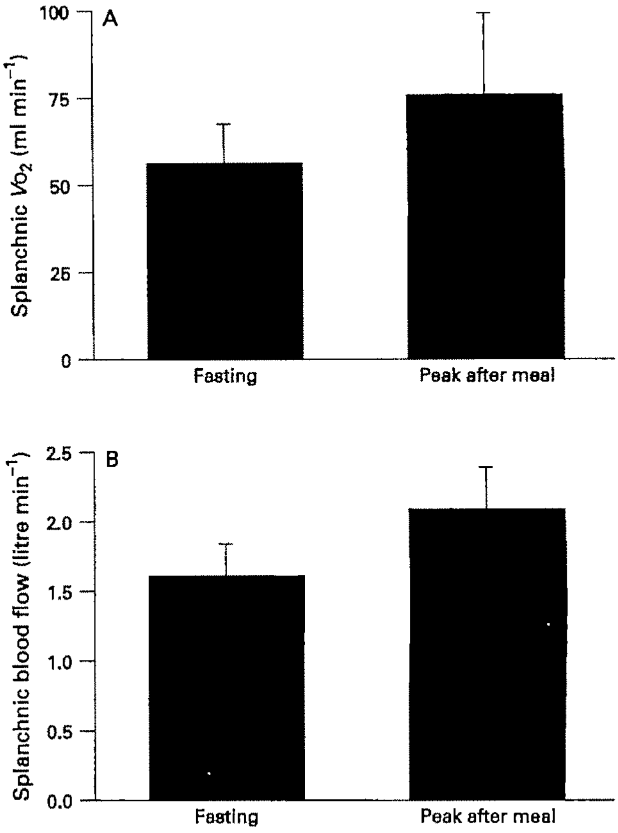

Figure 2 Effect of feeding on splanchnic blood flow and oxygen consumption in healthy subjects [data adapted from ref. 34]. A: Peak splanchnic oxygen consumption following a standard meal (mean (SD)). B: Peak splanchnic blood flow following a standard meal (mean (SD)).

Intestinal blood pressure–flow autoregulation is much weaker than the autoregulation of, for example, renal blood flow [23]. When arterial pressure decreases, blood flow decreases despite a vasodilatory response. The autoregulation is enhanced by feeding: the blood flow is better maintained in response to a decrease in perfusion pressure in the fed state (i.e. with intraluminal food present) than in the starved condition.

The response of the intestinal vasculature to an increase in venous outflow pressure depends on the adequacy of perfusion [23, 68]. If perfusion is sufficient for metabolic needs, an increase in the venous pressure results in arteriolar vasoconstriction (myogenic control). If perfusion is poor and venous pressure increases, the vascular resistance decreases and the capillary density increases (metabolic control).

The gut blood flow has a distinct response to feeding [23]. Digestion results in pronounced postprandial hyperaemia (fig. 2). Several mechanisms are probably involved: a local reflex to the presence of luminal contents, the release of vasoactive gastrointestinal hormones (e.g. gastrin, secretin, cholecystokinin) and the increase in gut metabolism (metabolic control) [23, 34].

The extrinsic neural control of gut blood flow is limited primarily to the sympathetic nervous system.

Sympathetic nervous activity reduces gut blood flow by increasing the vascular resistance of the arteries and arterioles; the veins have more limited sympathetic innervation. During persisting stimulation, the blood flow starts to recover after initial reduction ("autoregulatory escape") [23, 65]. After the stimulation, blood flow increases transiently to a higher level than before the stimulation [23].

Catecholamines are the most important circulating endogenous vasoactive substances that influence the gut blood flow. Alpha-adrenoceptor stimulation results in vasoconstriction and beta-adrenoceptor stimulation in vasodilatation. Accordingly, noradrenaline with predominantly alpha-adrenoceptor activity can be expected to increase the intestinal vascular resistance, whereas the effects of adrenaline are dose-dependent: vasodilatation at low doses and vasoconstriction at increasing doses when alpha-stimulation predominates. The net effects of circulating catecholamines on gut blood flow depend on the concomitant effects on cardiac output [3, 23]. Vasopressin and angiotensin are both potent intestinal vasoconstrictors. Their physiological role in the control of gut blood flow is not certain. They may both be involved in the intestinal vasoconstriction in acute hypovolaemia, and also modulate the response to sympathetic nerve stimulation and noradrenaline [16, 23].

Hepatic blood flow

There are three principal determinants of hepatic blood flow. The vascular resistance across the intestine determines the mesenteric influx and thereby the portal venous flow. The hepatic arterial resistance determines the hepatic arterial flow. The intrahepatic portal venous resistance is less important, since the portal venous flow is mainly determined by the outflow from the intestine, that is the resistance across the intestine. Finally, the hydrodynamic interaction between the hepatic arterial and portal venous flow, as described before, tends to compensate for any change in one of the inflows to the liver by a reciprocal change in the other [6, 57]. The hydrodynamic interaction, also called the hepatic arterial buffer response, is regulated by adenosine [39].

Autoregulation has little importance in the regulation of hepatic arterial pressure-volume relationship; the relationship between the arterial pressure and the flow is approximately linear. The hepatic portal venous bed clearly lacks autoregulation and has a linear pressure–flow relationship [6, 57].

Sympathetic nervous activity is the principal neural mechanism that influences hepatic blood flow. Sympathetic nerve stimulation evokes an increase in the hepatic arterial and portal resistance. The arterial vasoconstriction is transient and has similar autoregulatory escape as the intestinal vasoconstriction. In contrast, the portal response has a slower onset, but the increase in resistance is sustained, once established [26, 57]. In addition to the changes in vascular resistances, sympathetic nerve stimulation also reduces the hepatic volume, probably via contraction of the hepatic capacitance vessels. The volume reduction has a slow onset, persists throughout the stimulation and recovers more slowly than it develops [7, 57].

Role of nitric oxide in splanchnic blood flow regulation

Recent experimental studies have demonstrated that nitric oxide is important in the maintenance of basal vasodilatation in the mesenteric vasculature and the hepatic artery [2, 44]. In an anaesthetized pig model, inhibition of nitric oxide synthesis (non-selective inhibition of both constitutive and inducible nitric oxide synthase) increased hepatic arterial resistance but had no effect on the portal vascular resistance, while the hepatic arterial autoregulation was enhanced. The hydrodynamic interaction between the hepatic arterial and portal vein blood flow (hepatic arterial buffer response) was present after nitric oxide inhibition. After administration of endotoxin, both the hepatic arterial buffer response and autoregulation were abolished, independent of nitric oxide. Inhibition of nitric oxide synthesis after endotoxin increased the resistance of both hepatic artery and portal vein [2]. This suggests that during experimental endotoxin shock, nitric oxide is important in preserving the blood flow across the splanchnic bed. While these observations cannot be directly extrapolated to human septic shock, they do suggest that non-selective nitric oxide inhibition in septic shock may improve blood pressure at the expense of splanchnic perfusion.

Splanchnic blood flow in patients at risk of multiple organ failure

Only very few studies with quantitative measurements of splanchnic blood flow in intensive care patients have been published [1, 10, 11, 22, 28, 29, 52–54, 62, 63, 69, 71–73, 76]. The results have clearly demonstrated that data obtained from experimental studies or more stable patients should be extrapolated to the intensive care patient with great caution. The determinants, clinical relevance and the time course of splanchnic blood flow abnormalities in patients at risk of multiple organ failure have not been well established.

All quantitative splanchnic blood flow studies in intensive care patients at risk of multiple organ failure deal with the total hepatosplanchnic blood flow as measured by the Fick principle [1, 10, 11, 22, 28, 29, 52–54, 62, 63, 69, 71–73, 76]. Gastrointestinal tonometry cannot be used as a surrogate measure of hepatosplanchnic blood flow, since there is no consistent relationship between splanchnic blood flow and measurements obtained by gastric tonometry [53, 54, 72, 73]. Hence, pH_i will be only discussed briefly in the context of response to therapy aimed at improving splanchnic perfusion.

The pathophysiology of splanchnic blood flow and inadequate splanchnic tissue perfusion in intensive care patients is multifactorial. Two substantially different patterns of changes in splanchnic blood flow and metabolic demand are common in intensive care patients: one observed in low flow states [38, 53,

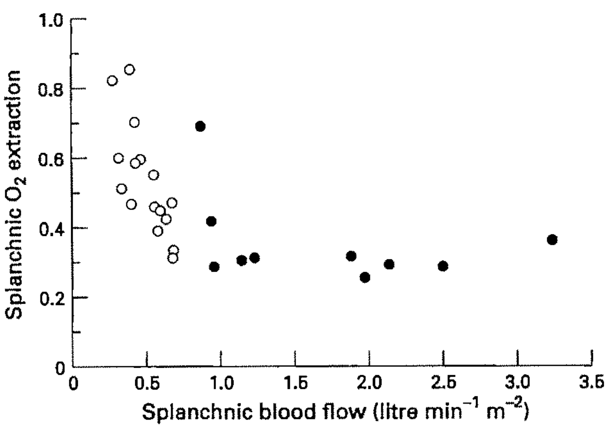

Figure 3 Splanchnic blood flow and oxygen extraction after cardiac surgery and in patients with septic shock and vasopressor therapy [data adapted from refs 62 and 63]. (○) After cardiac surgery; (●) septic shock + vasopressors.

54, 63, 64, 72, 73] and another in severe inflammatory conditions, infections and septic shock [1, 10, 11, 22, 28, 29, 62, 69, 76].

SPLANCHNIC BLOOD FLOW IN LOW FLOW STATES

In low flow states (e.g. cardiogenic shock) and hypovolaemia (without major injury or sepsis), splanchnic blood flow decreases without major changes in splanchnic metabolic demand [53, 54, 63, 72, 73]. In these conditions, perfusion of the heart and the central nervous system is maintained at the expense of the peripheral tissues and the splanchnic region. Once splanchnic vasoconstriction develops in response to hypovolaemia, the recovery of the blood flow will be prolonged: the increased splanchnic vascular resistance and reduced blood flow persists after the circulating blood volume has been restored and systemic haemodynamics have been stabilized [16]. This may increase the risk of inadequate splanchnic perfusion both after resuscitation of hypovolaemia and in intensive care patients susceptible to acute blood volume changes (e.g. as a result of capillary leak) [70].

In low flow states, vasoregulation is usually well preserved and an increased oxygen extraction compensates for the reduction of blood flow (fig. 3). Fully developed physiological compensation may preserve adequate splanchnic tissue oxygenation even during markedly reduced hepatosplanchnic blood flow. The limits of compensation and the time of tolerance for splanchnic hypoperfusion have not been well defined. Perioperative hepatic vein oxygen saturation below 30% during liver resection was associated with postoperative liver dysfunction [37], whereas brief exposure to lower hepatic venous saturation (or increased splanchnic oxygen extraction) have been reported during and after cardiac surgery without any major consequences [38, 53, 63, 64]. The splanchnic blood is defended at the expense of peripheral blood flow in low cardiac output syndrome after cardiac surgery [53, 63].

Nevertheless, prolonged hypovolaemia or low cardiac output will inevitably lead to splanchnic tissue hypoxia and increase the risk of multiple organ failure. It is reasonable to assume that a slowly developing low splanchnic blood flow is better tolerated than an acute reduction.

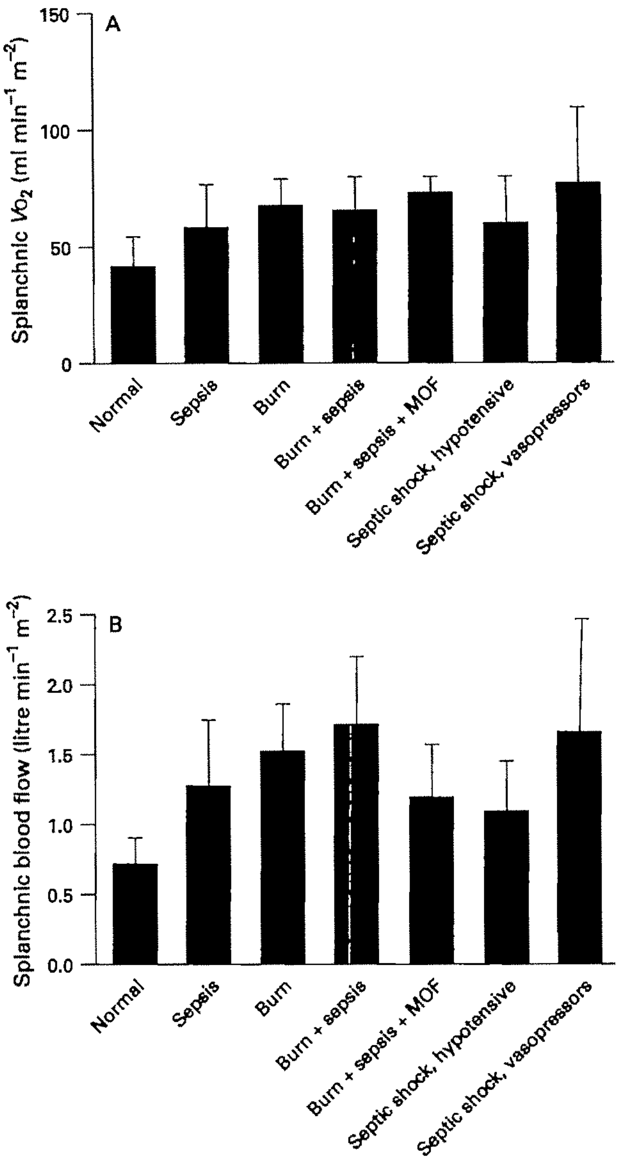

Figure 4 Increased splanchnic oxygen demand and blood flow in sepsis. A: Splanchnic hypermetabolism tends to increase with increasing severity of sepsis [data adapted from refs 11, 62 and 76]. B: Splanchnic blood flow and the severity of sepsis [data adapted from refs 11, 62 and 76].

SPLANCHNIC BLOOD FLOW IN INFLAMMATION AND INFECTION

In severe inflammation (e.g. systemic inflammatory response syndrome or SIRS, septic infections, septic shock), the metabolic demand for oxygen in the splanchnic region is increased [1, 10, 11, 22, 28, 29, 62, 69, 76]. In patients with normal or hyperdynamic haemodynamics, the total splanchnic blood flow is also higher than normal, but the increase in oxygen consumption is disproportionate to the increase in blood flow, and necessitates high oxygen extraction (figs 3 and 4). This appears to be the case regardless of whether stable haemodynamics have been obtained by fluids alone or with the aid of vasoactive

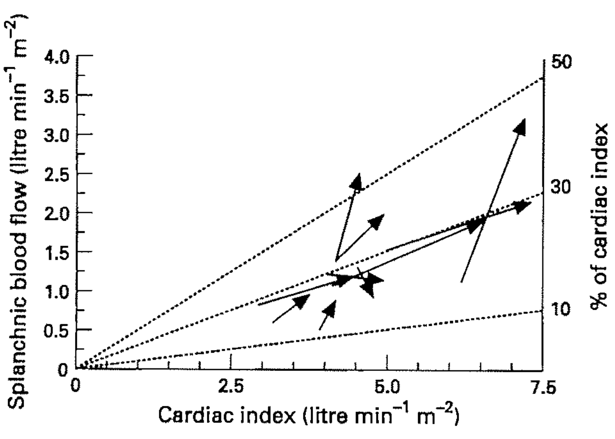

Figure 5 Changes in splanchnic blood flow in septic shock in response to treatment of hypotension with vasopressors [data adapted from ref. 62]. Wide interindividual variability is characteristic of the response.

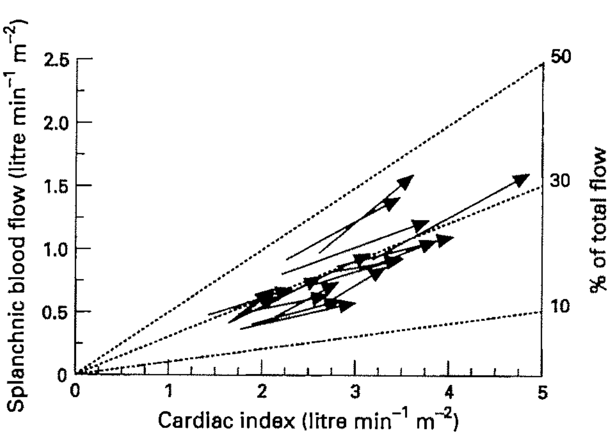

Figure 6 Changes in splanchnic blood flow in response to dobutamine after cardiac surgery [data adapted from ref. 53]. Splanchnic blood flow changes parallel the changes in cardiac output.

drugs [1, 10, 11, 22, 28, 29, 62, 69, 76]. In hyperdynamic septic shock during hypotension, splanchnic blood flow and splanchnic oxygen consumption are higher than normal and the splanchnic oxygen extraction is high [62]. Correction of hypotension by vasopressor drugs tends to increase the splanchnic blood flow further in hyperdynamic septic shock, although individual responses may vary (fig. 5) [62].

Endothelial injury is common in sepsis and contributes to abnormal vascular tone, blood flow maldistribution and development of hypovolaemia [8, 14, 46]. In addition, severe sepsis is almost invariably accompanied by acute respiratory failure, which limits the systemic oxygen delivery. Myocardial depression is also common in sepsis and many limit the response of systemic blood flow to the increased oxygen demand [51]. Under these circumstances, the splanchnic hypermetabolism increases the risk of splanchnic oxygen delivery/demand mismatch, and even subtle changes in blood volume, cardiac output, arterial oxygenation or oxygen demand in other tissues may lead to an imbalance between splanchnic oxygen delivery and demand.

THERAPEUTIC INTERVENTIONS AND SPLANCHNIC BLOOD FLOW

Volume resuscitation

The blood volume can be expected to have a major impact on splanchnic blood flow [13, 16, 55]. Indeed, reduction of splanchnic blood flow has been demonstrated in normal subjects after controlled small-volume haemorrhage [12, 56], and after simulated hypovolaemia following the application of lower body negative pressure [16]. Restoration of blood volume after simulated hypovolaemia was associated with a protracted reduction of splanchnic blood flow. Effects of blood volume on splanchnic blood flow in intensive care patients have not been published. Indirect data from studies using volume resuscitation to improve gastric pH_i suggests that restoration of blood volume is of primary importance in assuring adequate splanchnic perfusion in intensive care patients [32, 47–49].

Adrenergic agents

Vasoactive drugs, especially sympathomimetic amines are used frequently to support tissue perfusion in circulatory failure. The effects of sympathomimetic drugs on splanchnic blood flow in intensive care patients can not be predicted from their pharmacological characteristics alone or extrapolated from experimental models. Traditionally, the potential effects of adrenergic agents on regional perfusion have been interpreted in terms of their relative adrenergic receptor activity. In critically ill patients, the effects may be modified, for example as the result of receptor downregulation. In experimental studies, alpha-adrenergic stimulation by dopamine, noradrenaline and adrenaline increase renal and visceral vascular resistance and reduce renal and visceral blood flow [61]. The effects of dobutamine depend on the balance between its alpha-mediated vasoconstriction and beta-mediated vasodilatation [74]. Dopexamine with $beta_2$- and dopaminergic properties and without alpha-stimulation may have beneficial effects on splanchnic blood flow [41].

In 10 patients with septic shock, correction of hypotension by administration of vasopressor doses of dopamine increased splanchnic blood flow, whereas the effects of noradrenaline were more variable [62]. On the other hand, dopamine worsened gastric mucosal acidosis in septic shock, while noradrenaline resulted in increased gastric mucosal pH despite identical effects on systemic haemodynamics [43].

In patients with chronic congestive heart failure, dopexamine increased the splanchnic blood flow whereas neither dopamine nor dobutamine had an effect [40]. In contrast, both dobutamine and dopexamine consistently increased splanchnic blood flow immediately after cardiac surgery (figs 6 and 7) [53, 63, 72]. Despite the major increases in total splanchnic blood flow, both dobutamine and dopexamine lowered the gastric pH_i or failed to correct the gastric mucosal acidosis [53, 72]. These effects were even more prominent in patients with low cardiac output [53]. On the other hand, dobutamine corrected gastric mucosal acidosis in patients with

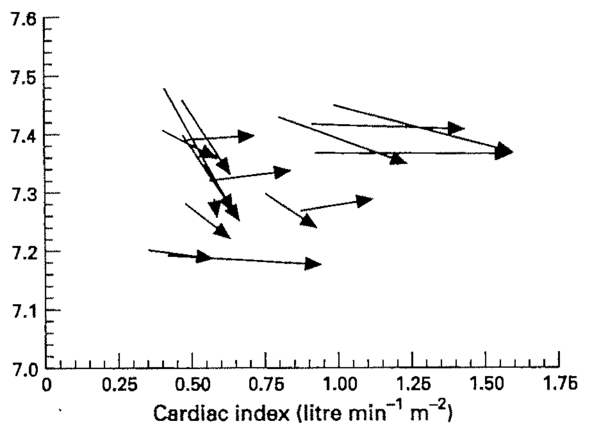

Figure 7 Changes in splanchnic blood flow and gastric pH_i in response to dobutamine after cardiac surgery [data adapted from ref. 53]. Gastric mucosal acidosis worsens especially in patients with low cardiac output despite the increased splanchnic blood flow.

sepsis [31]. Evidently, the underlying disease can modify the splanchnic blood flow responses to vasoactive drugs.

The cause for the decrease in gastric pH_i despite increased blood flow is not clear. The effects of a vasoactive drug may not be uniform throughout the splanchnic region: vasopressor therapy with dopamine or noradrenaline in experimental endotoxin shock increases regional vascular resistance of the colon, while the perfusion in the other parts of splanchnic region is well maintained [4]. The effects of vasoactive drugs on microcirculation may differ despite similar effects on blood flow distribution in major vessels [21]. Observations in experimental peritonitis support this concept: treatment with dobutamine produced more hepatocellular damage compared with dopexamine [75]. The catecholamines may also markedly modify the activity of various metabolic pathways in the liver [3] and simultaneously alter the splanchnic blood flow and its distribution. Accordingly, catecholamines may induce regional perfusion abnormalities and alter the balance between regional oxygen delivery and tissue metabolic demands.

Non-adrenergic vasodilators

The effects of vasodilators on splanchnic blood flow are controversial. Experimental studies suggest that vasodilators (adenosine and isoprenaline) may induce a vascular steal phenomenon within the intestinal circulation by redistributing the blood flow despite an overall increase [66].

In patients with chronic congestive heart failure, nitrates and sodium nitroprusside had no effect on the hepatosplanchnic blood flow despite increased cardiac output, indicating blood flow redistribution [40]. In contrast, sodium nitroprusside increased hepatosplanchnic blood flow in parallel with cardiac output in postoperative cardiac surgery patients [54]. Despite the increase in splanchnic blood flow, gastric pH_i decreased slightly.

Angiotensin converting enzyme inhibitors either had no effect or slightly reduced the hepatosplanchnic flow in cardiac failure [40]. After cardiac surgery, enalapril had no effect on either cardiac output or hepatosplanchnic blood flow, but reduced the gastric pH_i [52].

The effect of vasodilators on hepatosplanchnic blood flow or gastric pH_i have not been studied in septic patients. Nevertheless, the available data suggest that also the effects of vasodilators are modified markedly by the underlying clinical condition. It seems likely that redistribution of blood flow may occur at the level of both macro- and microcirculation.

References

1. Aulick LH, Goodwin jr CW, Becker RA, Wilmore DW. Visceral blood flow following thermal injury. *Annals of Surgery* 1981; **193**: 112–116.
2. Ayuse T, Brienza J, Revelly P, Boitnott JK, Robotham JL. Role of nitric oxide in porcine liver circulation under normal and endotoxemic conditions. *Journal of Applied Physiology* 1995; **78**: 1319–1329.
3. Bearn AG, Billing B, Sherlock S. The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. *Journal of Physiology* 1951; **115**: 430–441.
4. Breslow MJ, Miller CF, Parker SD, Walman AT, Traystman RJ. Effect of vasopressors on organ blood flow during endotoxin shock in pigs. *American Journal of Physiology* 1987; H291–H300.
5. Brundin T, Wahren J. Influence of a mixed meal on splanchnic and interscapular energy expenditure in humans. *American Journal of Physiology* 1991; **260**: E232–E237.
6. Bruns FJ, Fraley DS, Haigh J, Marquez JM, Martin DJ, Matuschak GM, Snyder JV. Control of organ blood flow. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in the Critically Ill.* Chicago: Year Book Medical Publishers, Inc, 1987: 87–124.
7. Carneiro JJ, Donald DE. Change in liver blood flow and blood content in dogs during direct and reflex alteration of hepatic sympathetic nerve activity. *Circulation Research* 1977; **40**: 150–158.
8. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple organ failure syndrome. *Archives of Surgery* 1986; **121**: 196–208.
9. Clements D, West R, Elias E. Comparison of bolus and infusion methods for estimating hepatic blood flow in patients with liver disease using indocyanine green. *Journal of Hepatology* 1987; **5**: 282–287.
10. Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA. Splanchnic and total body oxygen consumption differences in septic and injured patients. *Surgery* 1987; **101**: 69–80.
11. Dahn MS, Lange P, Wilson RF, Jacobs LA, Mitchell RA. Hepatic blood flow and splanchnic oxygen consumption measurements in clinical sepsis. *Surgery* 1990; **107**: 295–301.
12. Dalton JM, Gore DC, Makhoul RG, Fisher MR, DeMaria EJ. Decreased splanchnic perfusion measured by duplex ultrasound in humans undergoing small volume hemorrhage. *Critical Care Medicine* 1995; **23**: 491–497.
13. Darle N, Lim RC jr. Hepatic arterial and portal venous flows during hemorrhage. *European Surgical Research* 1975; **7**: 259–268.
14. Deitch EA. Multiple organ failure. Pathophysiology and potential future therapy. *Annals of Surgery* 1992; **216**: 117–134.
15. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19**: 1037–1040.
16. Edouard AR, Degrémont A-C, Duranteau J, Pussard E, Berdeaux A, Samii K. Heterogenous regional vascular responses to simulated transient hypovolemia in man. *Intensive Care Medicine* 1994; **20**: 414–420.
17. Ellis H. The gastrointestinal tract, the stomach. In: *Clinical*

Anatomy: a Revision and Applied Anatomy for Clinical Students. 6th ed. Oxford: Blackwell Scientific Publications, 1976: 73–98.

18. Fiddian Green RG, Amelin PM, Herrmann JB, Arous E, Cutler BS, Schiedler M, Wheeler HB, Baker S. Prediction of the development of sigmoid ischemia on the day of aortic operations. Indirect measurements of intramural pH in the colon. *Archives of Surgery* 1986; **121**: 654–660.
19. Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Critical Care Medicine* 1987; **15**: 153–156.
20. Fink MP, Kaups KL, Wang H, Rothschild HR. Maintenance of superior mesenteric arterial perfusion prevents increased intestinal permeability in endotoxic pigs. *Surgery* 1991; **110**: 154–161.
21. Giraud GD, MacCannell KL. Decreased nutrient blood flow during dopamine- and epinephrine-induced intestinal vasodilation. *Journal of Pharmacology and Experimental Therapeutics* 1984; **230**: 214–220.
22. Gottlieb ME, Sarfeh IJ, Stratton H, Goldman ML, Newell JC, Shah DM. Hepatic perfusion and splanchnic oxygen consumption in patients postinjury. *Journal of Trauma* 1983; **23**: 836–843.
23. Granger DN, Richardson PDI, Kvietys PR, Mortillaro NA. Intestinal blood flow. *Gastroenterology* 1980; **78**: 837–863.
24. Granger HJ, Norris CP. Intrinsic regulation of intestinal oxygenation in the anesthetized dog. *American Journal of Physiology* 1980; **238(7)**: H836–H843.
25. Granger HJ, Shepherd AP. Dynamics and control of the microcirculation. *Advances in Biomedical Engineering* 1979; **7**: 1–61.
26. Greenway CV, Oshiro G. Comparison of the effects of hepatic nerve stimulation on arterial flow, distribution of arterial and portal flows and the blood content in the livers of anaesthetized cats and dogs. *Journal of Physiology (London)* 1972; **227**: 487–501.
27. Grum CM, Fiddian-Green RG, Pittenger GL, Grant BJB, Rothman ED, Dantzker DR. Adequacy of tissue oxygenation in intact dog intestine. *Journal of Applied Physiology* 1984; **56**: 1065–1069.
28. Gump FE, Price JB jr, Kinney JM. Blood flow and oxygen consumption in patients with severe burns. *Surgery, Gynecology and Obstetrics* 1970; **130**: 23–28.
29. Gump FE, Price JB jr, Kinney JM. Whole body and splanchnic blood flow and oxygen consumption measurements in patients with intraperitoneal infection. *Annals of Surgery* 1970; **171**: 321–328.
30. Gutierrez G, Bismar H, Dantzker DR, Silva N. Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. *Critical Care Medicine* 1992; **20**: 451–457.
31. Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C. Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 324–9.
32. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, Klein F, San Roman E, Dorfman B, Shottlender J, Giniger R. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–199.
33. Haglund U, Hulten L, Åhren C, Lundgren O. Mucosal lesions in the human small intestine in shock. *Gut* 1975; **16**: 979–984.
34. Jensen MD, Johnson CM, Cryer PE, Murray MJ. Thermogenesis after a mixed meal: role of leg and splanchnic tissues in men and women. *American Journal of Physiology* 1995; **268**: E433–438.
35. Johnson PC. Myogenic nature of increase in intestinal vascular resistance with venous pressure elevation. *Circulation Research* 1959; **6**: 992–999.
36. Jorfeldt L, Juhlin-Dannfelt A. The influence of ethanol on splanchnic and skeletal muscle metabolism in man. *Metabolism* 1978; **27**: 97–106.
37. Kainuma M, Nakashima K, Sakuma I, Kawase M, Komatsu T, Shimada Y, Nimura Y, Nonami T. Hepatic venous hemoglobin oxygen saturation predicts liver dysfunction after hepatectomy. *Anesthesiology* 1992; **76**: 379–386.
38. Landow L, Phillips DA, Heard SO, Prevost D, Vandersalm TJ, Fink MP. Gastric tonometry and venous oximetry in cardiac surgery patients. *Critical Care Medicine* 1991; **19**: 1226–1233.
39. Lautt WW. Mechanism and role of intrinsic regulation of hepatic arterial blood flow: hepatic arterial buffer response. *American Journal of Physiology* 1985; **249**: G549–G556.
40. Leier CV. Regional blood flow responses to vasodilators and inotropes in congestive heart failure. *American Journal of Cardiology* 1988; **62**: 86E–93E.
41. Lokhandwala MF, Jandhyala BS. Effects of dopaminergic agonists on organ blood flow and function. *Clinical Intensive Care* (suppl) 1992; **3**: 12–15.
42. Lundgren O, Haglund U. The pathophysiology of the intestinal countercurrent exchanger. *Life Sciences* 1978; **23**: 1411–1422.
43. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *Journal of the American Medical Association* 1994; **272**: 1354–1357.
44. Mathie RT, Ralevic V, Alexander B, Burnstock G. Nitric oxide is the mediator of ATP-induced dilatation of the rabbit hepatic arterial vascular bed. *British Journal of Pharmacology* 1991; **103**: 1602–1606.
45. Matuschak GM. Liver-lung interactions in critical illness. *New Horizons* 1994; **2**: 488–504.
46. Matuschak GM. Oxidative stress and oxygen-dependent cytokine production. In: Vincent J-L, ed. *Yearbook of Intensive Care Medicine.* Berlin: Springer-Verlag, 1995.
47. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *Journal of the American Medical Association* 1993; **270**: 1203–1210.
48. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Medicine* 1994; **20**: 99–104.
49. Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. *Intensive Care Medicine* 1994; **20**: 203–209.
50. Nelson DP, Samsel RW, Wood LDH, Schumacker PT. Pathological supply dependence of systemic and intestinal O2 uptake during endotoxemia. *Journal of Applied Physiology* 1988; **64**: 2410–2419.
51. Parker MM, Shelhelmer JH, Bacharach SL, Green MV, Natanson C, Fredrick TM, Damske RN, Parrillo JE. Profound but reversible myocardial depression in patients with septic shock. *Annals of Internal Medicine* 1984; **100**: 483–490.
52. Parviainen I, Rantala A, Ruokonen E, Takala J. Failure of enalaprilat to reduce blood pressure in hypertensive cardiac surgery patients. *Critical Care Medicine* 1995; **23** (Suppl): A140.
53. Parviainen I, Ruokonen E, Takala J. Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. *British Journal of Anaesthesia* 1995; 74: 277–282.
54. Parviainen I, Ruokonen E, Takala J. Sodium nitroprusside after cardiac surgery: central and regional hemodynamics. *Acta Anaesthesiologica Scandinavica* (in press).
55. Peitzman A. Principles of circulatory support and the treatment of hemorrhagic shock. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in the Critically Ill.* Chicago: Year Book Medical Publishers, Inc., 1987: 407–418.
56. Price HL, Deutsch S, Marshall BE, Stephen GW, Behar MG, Neufeld GR. Hemodynamic and metabolic effects of hemorrhage in man with particular reference to the splanchnic circulation. *Circulation Research* 1966; **18**: 469–474.
57. Richardson PDI, Withrington PG. Liver blood flow. Intrinsic and nervous control of liver blood flow. *Gastroenterology* 1981; **81**: 159–173.
58. Rowell LB, Blackmon JR, Kenny MA, Escourrou P. Splanchnic vasomotor and metabolic adjustments to hypoxia and exercise in humans. *American Journal of Physiology* 1984; **247**: H251–H258.
59. Rowell LB, Brengelmann GL, Blackmon JR, Twiss RD, Kusumi F. Splanchnic blood flow and metabolism in heat-stressed man. *Journal of Applied Physiology* 1968; **24**: 475–484.
60. Rowell LB, Detry J-MR, Blackmon JR, Wyss C. Importance

of the splanchnic vascular bed in human blood pressure regulation. *Journal of Applied Physiology* 1972; **32**: 213–220.
61. Ruffolo RR Jr, Fondacaro JD, Levitt B, Edwards RM, Kinter LB. Pharmacologic manipulation of regional blood flow. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in Critically Ill*. 1st ed. Chicago: Year Book Medical Publishers, 1987: 450–474.
62. Ruokonen E, Takala J, Kari A, Saxén H, Mertsola J, Hansen EJ. Regional blood flow and oxygen transport in septic shock. *Critical Care Medicine* 1993; **21**: 1296–1303.
63. Ruokonen E, Takala J, Kari A. Regional blood flow and oxygen transport in low cardiac output syndrome after cardiac surgery. *Critical Care Medicine* 1993; **21**: 1304–1311.
64. Ruokonen E, Takala J, Uusaro A. Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. *Critical Care Medicine* 1991; **19**: 1365–1369.
65. Shepherd AP, Granger HJ. Autoregulatory escape in the gut: a systems analysis. *Gastroenterology* 1973; **65**: 77–91.
66. Shepherd AP, Riedel GL, Maxwell LC, Kiel JW. Selective vasodilators redistribute intestinal blood flow and depress oxygen uptake. *American Journal of Physiology* 1984; **247**: G377–384.
67. Shepherd AP. Intestinal blood flow autoregulation during foodstuff absorption. *American Journal of Physiology* 1980; **8**: H156–H162.
68. Shepherd AP. Myogenic responses of intestinal resistance and exchange vessels. *American Journal of Physiology* 1977; **233**: H547–554.
69. Steffes CP, Dahn MS, Lange MP. Oxygen transport-dependent splanchnic metabolism in the sepsis syndrome. *Archives of Surgery* 1994: **129**: 46–52.
70. Takala J. Splanchnic perfusion in shock. *Intensive Care Medicine* 1994; **20**: 403–404.
71. Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. *Cardiovascular Research* 1995; **30**: 106–112.
72. Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect change in splanchnic blood flow after cardiac surgery. *British Journal of Anaesthesia* 1995; **74**: 149–154.
73. Uusaro A, Ruokonen E, Takala J. Splanchnic oxygen transport after cardiac surgery: evidence for inadequate tissue perfusion after stabilization of hemodynamics. *Intensive Care Medicine* 1996; **22**: 26–33.
74. Vernon DD, Garret JS, Banner W jr, Dean JM. Hemodynamic effects of dobutamine in an intact animal model. *Critical Care Medicine* 1992; **20**: 1322–1329.
75. Webb AR, Moss RF, Tighe D, Al-Saady N, Bennett ED. The effects of dobutamine, dopexamine and fluid on hepatic histological responses to porcine faecal peritonitis. *Intensive Care Medicine* 1991; **17**: 487–493.
76. Wilmore DW, Goodwin CW, Aulick LH, Powanda MC, Mason AD, Pruitt jr MD. Effect of injury and infection on visceral metabolism and circulation. *Annals of Surgery* 1980; **192**: 491–500.
77. Winsö O, Biber B, Gustavsson B, Holm C, Milsom I, Niemand D. Portal blood flow in man during graded positive end-expiratory pressure ventilation. *Intensive Care Medicine* 1986; **12**: 80–85.
78. Zhang H, Spapen H, Manikis P, Rogiers P, Metz G, Buurman WA, Vincent J-L. Tirilazad mesylate (U-74006F) inhibits effects of endotoxin in dogs. *American Journal of Physiology* 1995; **268**: H1847–H1855.

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Splanchnic ischaemia/reperfusion and multiple organ failure

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Multiple organ failure (MOF) remains the leading cause of delayed mortality in surgical intensive care units. A recent epidemiological review revealed that 61% of late deaths in our trauma centre were the result of organ failure [117]. Once established, MOF defies our standard critical care supportive measures: mortality ranges from 40–100%, and is related directly to the number and duration of organ failures [65]. Unfortunately, basic laboratory investigations have been hampered by a lack of understanding of its underlying pathophysiology. As a result, neither the incidence nor the mortality of the syndrome has improved significantly in recent years. Our trauma research centre has actively sought to define and characterize MOF, and to elucidate the mechanisms responsible for its progression. This review will attempt to highlight our current knowledge, particularly with regard to the role of splanchnic ischaemia and reperfusion (I/R) in MOF. It is our hope that by identifying pathogenetic mechanisms of MOF, we may ultimately be able to design and time therapeutic interventions to prevent or reverse the deadly process.

Historical perspective

MOF has been called a "syndrome of surgical progress", as its emergence appears to have been a direct result of our ability to manage single-organ failures successfully. Significant refinements in surgical technique and perioperative care have often occurred during times of war, owing to the availability of larger, more concentrated experiences. For example, in the First World War, "wound shock", or a deficiency of circulating blood volume, was a common cause of death. Studies performed in the post-war period demonstrated the role of acute blood loss in the pathogenesis of traumatic shock, leading to more widespread use of blood transfusions [21]. Not surprisingly, the aggressive administration of blood in the Second World War was credited with the reduced early mortality from shock. However, reports at the end of the Second World War noted that many of the wounded went on to develop acute renal failure. This continued to be a problem during the Korean War. In fact, among those wounded in Korea who reached forward hospitals alive, renal failure was blamed for over 50% of later fatalities [127]. Basic scientific investigations supported the addition of crystalloid solutions to blood transfusions. More vigorous fluid resuscitation during the Vietnam War led to a 20- to 30-fold reduction in the incidence of renal failure compared with the Korean experience. However, a new problem came to the forefront in Vietnam: "shock lung"—the acute respiratory distress syndrome (ARDS) [8]. Of note, in accounts of the Korean conflict, there was virtually no mention of pulmonary problems. Advances in respiratory care, and particularly in mechanical ventilation, allowed more patients to survive ARDS. Today, while our ability to sustain patients on mechanical ventilation has improved, the number of patients dying with ARDS remains high; this is because the actual cause of death has shifted to MOF. The identification of MOF as a distinct entity dates back to 1973, when Tilney, Bailey and Morgan [128] described the progressive failure of organ systems in patients following repair of ruptured abdominal aortic aneurysms. Baue [15] first suggested there was a sequential pattern to the MOF syndrome. In 1977, Eiseman, Beart and Norton [40] at our institution described its clinical presentation and coined the term "multiple organ failure". Since that time, intensive research efforts have targeted the syndrome.

Multiple organ failure syndrome

Regardless of the inciting event, the syndrome of MOF generally follows a predictable course. Typically, ARDS is first, followed by renal and hepatic dysfunction. Myocardial failure is a later (and often preterminal) manifestation. The reason for the early appearance of pulmonary failure is unclear; it may reflect a lesser functional reserve of the lung compared with liver or kidneys, or it may suggest that our ability to detect pulmonary dysfunction is more sensitive. The time course of MOF is variable, as it may be affected by the nature of the initial insult as well as by pre-existing disease. We have recently recognized a bimodal pattern in the development of MOF in a large series of severely injured patients, with distinct characteristics of each group [91]. Early

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Key words
Heart, ischaemia. Complications, multiple organ failure.

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Table 1 Multiple organ failure (MOF) score*

	Organ	Grade 1	Grade 2	Grade 3
A	Lung	ARDS score > 5†	ARDS score > 9	ARDS score > 13
B	Kidney	Creatinine > 1.8‡	Creatinine > 2.5	Creatinine > 5.0
C	Liver	Bilirubin > 2.0§	Bilirubin > 4.0	Bilirubin > 8.0
D	Heart	Minimal inotropes**	Moderate inotropes	High inotropes

*MOF score = grade (A+B+C+D) not due to chronic disease.

†See table 2 for ARDS score.

‡Creatinine (mg dl^{-1}).

§Bilirubin (not due to biliary obstruction or resolving haematoma) in mg dl^{-1}.

**Cardiac index < 3 litre min^{-1} m^{-2} requiring inotropic support: minimal = dopamine or dobutamine < 5 µg kg^{-1} min^{-1}; moderate = 5–15 µg kg^{-1} min^{-1}; high = > 15 µg kg^{-1} min^{-1}.

Table 2 Acute respiratory distress syndrome (ARDS) score*

	Parameter	Grade 1	Grade 2	Grade 3	Grade 4
A	Chest x-ray	Diffuse, mild interstitial consolidation	Diffuse, marked interstitial/mild airspace consolidation	Diffuse, moderate airspace consolidation	Diffuse, severe airspace consolidation
B	Pa_{O_2}/FI_{O_2} (torr)	175–250	125–174	80–124	< 80
C	Ve (litre min^{-1})	11–13	14–16	17–20	> 20
D	PEEP (cm H_2O)	6–9	10–13	14–17	> 17
E	Cstat (ml cm^{-1} H_2O)	40–50	30–39	17–20	< 20

Pa_{O_2}/FI_{O_2} = ratio of arterial oxygen tension to fractional inspired oxygen concentration; Ve = minute ventilation; PEEP = positive end-expiratory pressure; Cstat = static compliance.

*ARDS score = grade A (A+B+C+D+E) provided no clinical suspicion of pulmonary oedema.

MOF (occurring within 72 h of the initial insult) appears to be associated with more cardiac dysfunction, and indices of shock are the critical risk factors. In addition, it takes a rapid course: those patients who die, succumb faster. In contrast, late MOF (> 72 h after the initial insult) is associated with more hepatic dysfunction and advanced age. Infections appear to be more prominent in its pathogenesis, and non-surviving patients suffer a protracted course.

To identify organ failure more precisely, numerous scoring and classification schemes have been applied to MOF [42, 46, 64]; a discussion of them is beyond the scope of this review. When we initiated our National Institutes of Health (NIH) Specialized Centers of Research (SCOR) project in 1987, we developed an MOF score for the purpose of identifying MOF as an endpoint, objectively and reproducibly. We initially experienced difficulties in applying the score in a multicentre trial, and subsequently revised it [115]. Our MOF score is now based on easily obtainable measurements of pulmonary, renal, hepatic and cardiovascular function (tables 1 and 2). Individual organ failure is defined as a grade of 2 or higher, and MOF is defined as a score of 4 or more, 48 h after admission. We do not consider scores in the first 48 h because they may reflect reversible derangements induced by the inciting event or by incomplete resuscitation. Gastrointestinal, haematological, neurological and metabolic failure—included in the original score—were excluded from consideration because their definitions were subjective and, more importantly, they did not contribute substantially to identifying MOF. Applying the MOF score in our critically ill patients has greatly facilitated our clinical research efforts, particularly in identifying risk factors for MOF [116]. Consequently, we have been able to focus our basic research effort on the highest-risk patients, characterizing many of the physiological derangements associated with severe injury and correlating them with the progression to MOF. Further, we have been able to develop laboratory models to mimic severe injury *in vivo*, and manipulate the inflammatory response *in vitro*.

Pathogenesis of multiple organ failure

INFECTION AND MULTIPLE ORGAN FAILURE

Early reports of MOF implicated infection as the primary aetiological factor [109]. An influential paper by Fry and colleagues [46] in 1980 retrospectively reviewed 553 patients requiring emergent operations. Thirty-eight (7%) developed MOF; of these, 89% had sepsis, leading the investigators to conclude that MOF was a "fatal expression of uncontrolled infection". This study was pivotal in the subsequent adoption of an aggressive policy of mandatory laparotomy to drain intra-abdominal abscesses in MOF patients. This seemed a rational approach at the time, particularly since the primary experiences being reported were from urban trauma centres, in which penetrating injuries were frequently complicated by secondary infections. However, a provocative paper by Norton [98] in 1985 showed that drainage of intra-abdominal abscesses resulted in reversal of MOF in a dishearteningly small number of patients. Thus, it appeared that an abscess may promote MOF but was not necessary to perpetuate it. An alternative viewpoint was offered in reports from Europe around this time, which emphasized that a large number of patients with clinical sepsis could develop MOF and die without a focus of infection. Faist and colleagues [42] reviewed 433 trauma patients, of whom 8 % developed MOF; of these, only 59 % had sepsis. Goris and colleagues [50] examined the role of sepsis in MOF. Bacterial sepsis was confirmed in just 33 % of trauma patients, compared with 45 % of intra-abdominal sepsis (non-trauma) patients.

Continuing with the theme of infection as the aetiological agent of MOF, Marshall and colleagues [76] analysed nosocomial infections bacteriologically and concluded that the proximal gastrointestinal tract was the occult source of infection. Indeed, extensive basic research, employing a variety of rodent models, offered compelling evidence invoking translocation of bacteria or endotoxin as the common precipitating event for MOF after injury or haemorrhagic shock [12, 35, 73, 120]. However, considerable debate has centred around whether microbial translocation is a clinically important phenomenon [95]. We performed a prospective clinical trial to verify bacterial translocation in 29 patients sustaining major trauma [90]. In this patient population (with a 30 % incidence of MOF), we were unable to detect bacteria in either portal or systemic circulation within the first 5 days after injury. In addition, we found no elevations of tumour necrosis factor (TNF) to suggest endotoxaemia. Similar findings were reported by other contemporary investigators. Peitzman and colleagues [104] found no evidence of bacterial translocation in 25 injured patients, despite a mortality of 16 % and a 40 % major complication rate. Morales and colleagues [92] found no evidence of translocation in a porcine model of haemorrhagic shock. Additional evidence minimizing the contribution of translocation came from trials using selective gut decontamination to suppress intestinal aerobic flora (and thereby limit the translocation of microbes). This intervention has not proved beneficial in reducing MOF or mortality [28, 51]. Thus, while early studies correctly observed that infection with systemic sepsis can cause MOF, MOF frequently occurs in the absence of infection. Based on these findings, our investigations were redirected towards elucidating alternative mechanisms promoting the postinjury systemic inflammatory response syndrome (SIRS) and ultimately MOF.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The systemic clinical manifestations of Gram-negative bacterial sepsis can be mimicked by other infectious organisms, as well as by stimuli that lead to a prolonged and excessive inflammatory response. To standardize communication in this area, a consensus paper by the American College of Chest Physicians/Society of Critical Care Medicine proposed definitions pertaining to sepsis and organ failure [32]. The term "SIRS" refers to the inflammatory response to infectious or non-infectious processes. SIRS is defined as two or more of the following clinical conditions, independent of cause: (1) body temperature > 38 °C or < 36 °C; (2) heart rate > 90 beat/min; (3) tachypnoea, manifest by respiratory rate > 20 breaths/min or hyperventilation indicated by $Pa_{CO_2} < 32$ torr; (4) alteration of the white blood cell count with $> 12 \times 10^6$ cells/l or $< 4 \times 10^6$ cells/l. "Sepsis" refers to SIRS of an infectious origin. The recognition of SIRS independent of infection has stimulated several new hypotheses regarding the underlying mechanism of MOF. The focus of recent thought is that MOF represents the culmination of a generalized and excessive neuroendocrine, immune and inflammatory response to an insult—a modern "horror autotoxicus" [16].

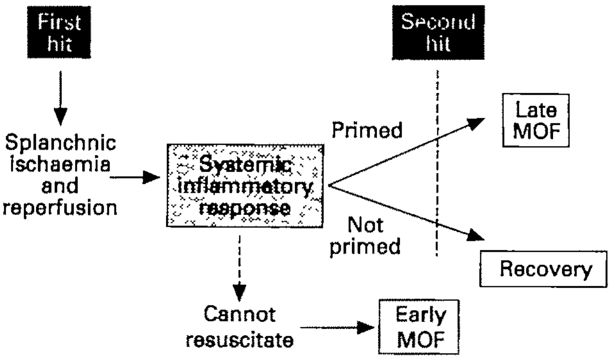

Figure 1 The "two-hit" model of postinjury multiple organ failure (MOF). The initial insult (first hit) causes splanchnic hypoperfusion, resulting in systemic inflammatory response syndrome. Some patients immediately progress to early MOF; others are "primed" such that a second hit results in progression to late MOF.

THE "TWO-HIT" MODEL OF MULTIPLE ORGAN FAILURE

The realization that the host is destroying itself, and is not being consumed by micro-organisms, shifted research efforts from the detection and treatment of infections to characterization and attenuation of the initial insult. Our SCOR project proposed a "two-hit" model of MOF several years ago (fig. 1). Briefly, an initial insult (the "first hit") "primes" the inflammatory system such that the response of the system to a second insult (the "second hit") is exaggerated. This exaggerated response can precipitate MOF. The correlate of this model at the cellular level is the priming and activation of polymorphonuclear leucocytes—neutrophils (PMN) [23]. The second hit may be virtually any insult, including infection, anaesthesia, an episode of hypotension, etc. In some cases, the patient suffers such a massive first hit that he or she deteriorates rapidly into MOF.

Our trauma research centre has examined the underlying pathophysiology of the first hit, and attempted to identify indicators of primed patients who are at risk for MOF after a second hit. A number of diverse clinical conditions have been reported to precede the progression to MOF (i.e. first hits); in general, the insults may be classified as infection, inadequate tissue perfusion, inflammation, or dead or injured tissue. Consequently, there are several existing hypotheses regarding what constitutes the first hit, although none have been accepted wholeheartedly. One prominent theory is the "gut hypothesis", which suggests that the gut is the "motor of MOF" [84].

Splanchnic ischaemia/reperfusion

The splanchnic circulation is particularly vulnerable to hypoperfusion. Several investigators have demonstrated that in low-flow states such as haemorrhagic shock, perfusion of the splanchnic bed decreases dramatically and out of proportion to the overall decrease in cardiac output [2, 11, 82]. Furthermore, the splanchnic circulation is the last to be restored after resuscitation. Gastric intramucosal pH measurements have a high specificity for predicting patient survival in the intensive care unit [38]. Maynard and colleagues [79] found gastric intramucosal pH to be an earlier and more reliable predictor of outcome than cardiac index, oxygen delivery or oxygen consumption, prompting Dantzker [34] to refer to the gastrointestinal tract as "the canary of the body".

The mechanism of disproportionate splanchnic vasoconstriction is probably multifactorial. Autonomic (neurally mediated α-adrenergic stimulation of postcapillary venous beds), humoral (vasopressin and angiotensin II), and local factors (prostaglandins $PGF_{2\alpha}$, PGB_2 and PGD_2, leukotrienes C_4 and D_4, some thromboxane analogues and nitric oxide inhibition) all appear to be involved. In addition, motor activity and luminal distension can cause hypoperfusion of intestinal segments [74, 103]. The relative contribution of each factor is unclear. Although there is increased sympathetic nervous system activity in low-flow states, disproportionate splanchnic vasoconstriction is not ameliorated by α-adrenergic block [82] or mesenteric arterial denervation [2]. In contrast, the vasoconstriction can be abrogated by pharmacological or surgical ablation of the renin–angiotensin axis, suggesting a primary role of the axis in mediating the effect [11].

Tissue ischaemia initiates a sequence of events that may ultimately lead to cellular dysfunction and necrosis. The primary mechanism is depletion of cellular energy stores and accumulation of toxic metabolites. Resumption of blood flow is necessary for cellular salvage; however, reperfusion of ischaemic tissues paradoxically creates more tissue injury. In fact, Parks and Granger [102] have shown that relatively little intestinal mucosal injury occurs during ischaemia compared with reperfusion. Interestingly, anoxic reperfusion of ischaemic tissues results in very little damage, suggesting that the formation of oxygen-derived cytotoxic products is critical in I/R injury [72, 105].

REACTIVE OXYGEN METABOLITES IN REPERFUSION INJURY

Molecular oxygen (O_2) can accept a total of four electrons to form water (H_2O); however, stepwise reduction of O_2 generates different species of oxidants. The univalent reduction of O_2 yields the superoxide anion radical (O_2^-). The cellular toxicity of O_2^- is attributed to its role as a precursor of more reactive species. Hydrogen peroxide (H_2O_2) is formed as a result of the divalent reduction of O_2, or the dismutation of O_2^-. The latter occurs spontaneously and rapidly in aqueous solution, so that the production of O_2^- is generally associated with the generation of H_2O_2.

Finally, through the Haber-Weiss reaction, O_2^- and H_2O_2 interact to produce the hydroxyl radical (•OH), the most potent known oxidizing agent [136]. The result of the formation of these reactive oxygen metabolites (ROM) is damage to membrane lipids, nucleic acids, enzymes and receptors, with impaired cellular function and eventual necrosis [121]. The formation of ROM after reperfusion has been detected using electron-spin resonance spectrometry [97] and chemiluminescence [129]. These studies demonstrate a burst of ROM formation immediately after reperfusion, lasting 2–5 min. Free radical scavengers such as superoxide dismutase (SOD) can suppress the respiratory burst. The ROM generated during reperfusion have been directly implicated in tissue injury. Increases in microvascular permeability induced by I/R can be attenuated by SOD, copper diisopropyl salicylate (an SOD mimetic), calatase (an enzyme that catalyses H_2O_2 disproportionately to H_2O and O_2), and non-enzymatic scavengers of •OH including dimethyl sulphoxide, dimethyl thiourea and mannitol [136].

XANTHINE OXIDASE IN REPERFUSION INJURY

Xanthine oxidase (XO) is the rate-limiting enzyme in nucleic acid degradation, through which all purines are channelled for terminal oxidation. XO can generate O_2^- and H_2O_2 during the oxidation of hypoxanthine or xanthine. In healthy, non-ischaemic cells XO exists predominantly as the NAD^+-dependent xanthine dehydrogenase (XD), which does not use O_2 as an electron acceptor and thus does not produce O_2^- or H_2O_2. During tissue ischaemia, XD is converted to XO [14]. In comparison with other tissues, the intestinal mucosa has a tremendous capacity to oxidize hypoxanthine via XO. In fact, in humans, liver and intestine have the highest XO activity of any tissue [52]. The role of XO in intestinal reperfusion injury has been directly assessed. The XO inhibitors allopurinol, oxypurinol and pterin aldehyde all attenuate I/R-induced microvascular permeability. In addition, XO inactivation by adminstration of a tungsten-supplemented, molybdenum-deficient diet (tungsten replaces molybdenum in the active site of XO, rendering it inactive) has the same effect [136].

NEUTROPHILS IN REPERFUSION INJURY

Neutrophils (PMN) represent another source of ROM. NADPH oxidase in PMN reduces O_2 to O_2^-. In addition, PMN-derived myeloperoxidase catalyses the formation of hypochlorous acid (HOCl) from chloride ions and H_2O_2. HOCl is approximately 100 times as reactive as H_2O_2 as an oxidizing and chlorinating agent. It reacts with primary amines to form N-chloro derivatives, potent oxidizing agents which are likely mediators of cellular injury [136].

The potential role of PMN in reperfusion injury has been studied extensively. PMN exist in high concentrations in intestinal mucosal tissue (10^6 PMN/g tissue) [52]. This population of cells is capable of producing enough O_2^- and cytotoxic enzymes (e.g. elastase, collagenase) to injure or destroy parenchymal and endothelial cells. Ischaemia and, to a greater degree, reperfusion of intestine lead to a large influx of PMN. Based on pretreatment with various compounds, it appears that ROM play a role in PMN recruitment [54, 125]. Hernandez and colleagues [55] demonstrated that PMN are the primary mediators of I/R-induced intestinal microvascular permeability. They further identified PMN–endothelial adhesion via the PMN CD18 membrane receptor as an essential component of I/R injury. Using intravital microscopy, Granger and colleagues [53] observed that I/R greatly exacerbates PMN-endothelial adhesion over ischaemia alone, and demonstrated that XO-derived ROM initiate the adherence of PMN to endothelium.

The above studies have provided a framework for intestinal I/R injury: I/R results in the generation of ROM which play a role in attracting PMN to the intestinal microvasculature, promoting adherence to the endothelium, and allowing PMN-mediated tissue injury with increased microvascular permeability. We became interested in this sequence of events as it related to distant organ injury.

Splanchnic ischaemia/reperfusion as a model of systemic inflammation

Although a number of inflammatory cascades have been incriminated in the pathogenesis of MOF, an attractive unifying concept is diffuse PMN-mediated tissue injury. The PMN is well equipped for cytotoxicity via oxygen dependent (NADPH oxidase) and independent (proteolytic enzymes) mechanisms, and PMN have been incriminated directly in the pathogenesis of ARDS and MOF [99, 126, 133]. PMN can be activated by I/R [25, 45, 49], and they have been demonstrated in distant organs following I/R insults [6, 118, 130]. Thus, we hypothesized that after injury splanchnic I/R creates a local environment that primes circulating PMN which mediate distant organ injury.

We developed a rodent model of splanchnic I/R [107]. In brief, adult, mature Sprague–Dawley rats (350–400 g) were anaesthetized and via a midline laparotomy the superior mesenteric artery (SMA) was occluded at its origin. After 45 min of intestinal ischaemia, the clamp was removed, the incision was closed and the animals were allowed to wake. The 45-min clamp time was based on preliminary studies demonstrating 100 % survival and no intestinal mucosal histological changes at 24 h. We found that splanchnic I/R results in reversible liver and lung injury (as measured by microvascular permeability). This effect was not seen in PMN-depleted rodents, implicating PMN in the injury. Work before this in our laboratory had shown that depletion of XO activity by tungsten diet decreased lung PMN accumulation following haemorrhagic shock [5]. We were interested in the role of XO in our I/R model, and repeated the experiments with the I/R insult. We found that XO inactivation, like PMN depletion, abrogated the effects of I/R on distant organs [108]. In attempting to sequence the events after splanchnic I/R, we identified XO activation as a proximal event, whose blockade attenuated splanchnic PMN accumulation, circulating PMN priming and lung injury [71].

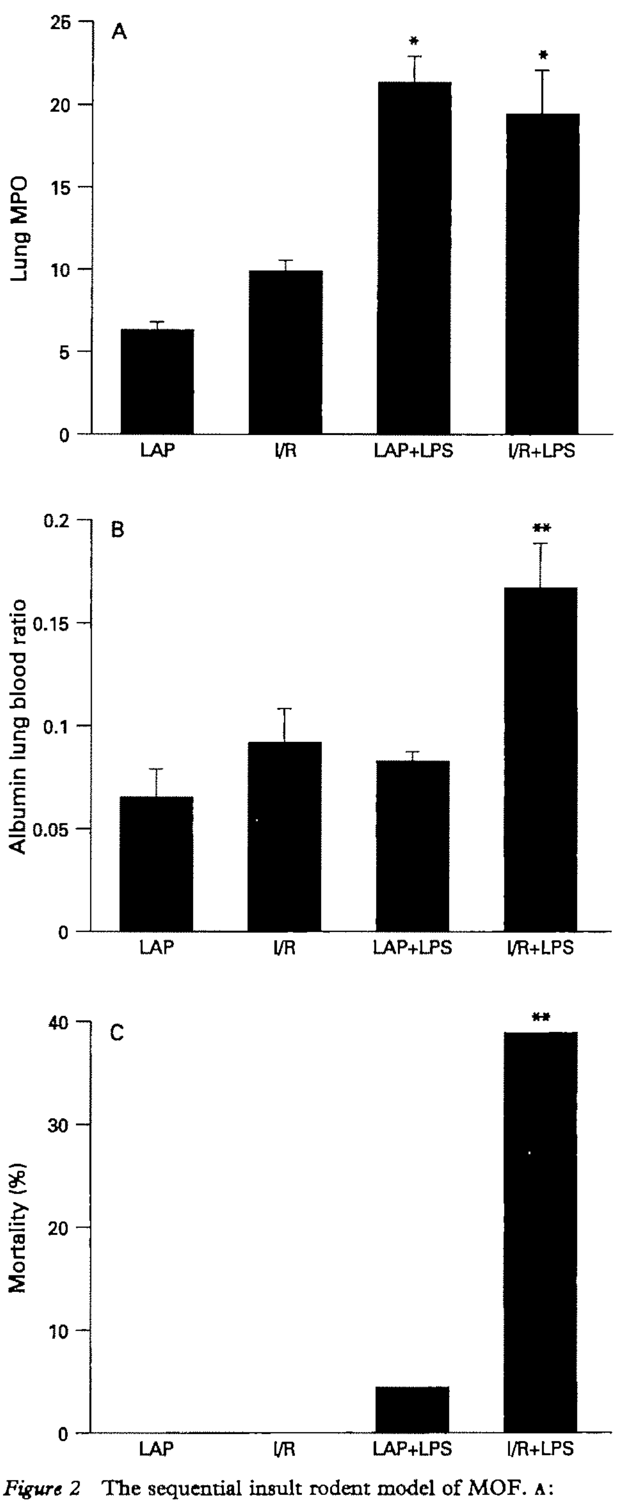

Figure 2 The sequential insult rodent model of MOF. A: Laparotomy (LAP) or laparotomy with splanchnic ischaemia and reperfusion (I/R) were performed alone, or followed in 6 h by lipopolysaccharide (LPS) (LAP+LPS or I/R+LPS). LPS resulting in polymorphonuclear leucocyte sequestration with or without I/R. Sequential results (I/R followed by LPS) resulted in increases in lung leak (B) and mortality (C). *Denotes difference from LAP and I/R; **denotes difference from LAP, I/R, and LAP+LPS ($P < 0.05$).

Clinical experience indicated that multiple insults (the two-hit model) were more typical of MOF.

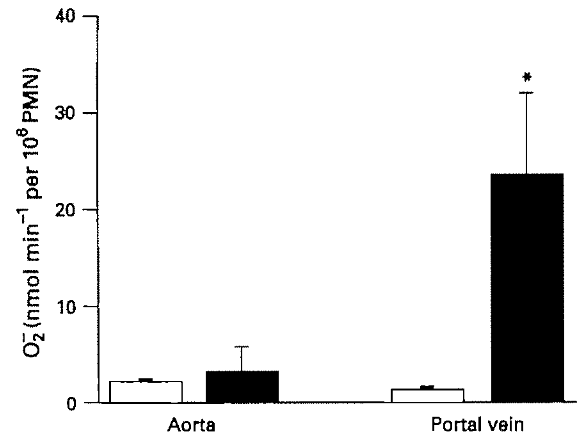

Figure 3 Priming of polymorphonuclear leucocytes (PMN) in the portal *vs* systemic circulation after splanchnic I/R, at 90 min of reperfusion. Priming measured as superoxide generation following formyl-methionyl-leucyl-phenylalanine (fMLP) stimulation. *Denotes difference from aortic samples. (□) −fMLP; (■) +fMLP.

Thus, our working hypothesis became that splanchnic I/R initially primes the systemic inflammatory cascade, and when followed by an activating stimulus during the vulnerable "primed" period, results in distant organ injury. To test this hypothesis, we developed a sequential insult model in which the priming event was splanchnic I/R, and the activating event was injection with low-dose endotoxin. Six hours into reperfusion, the study animals were administered low-dose bacterial lipopolysaccharide (LPS) (*Salmonella typhimurium*), 2.5 mg kg^{-1} i.p. The LPS dose was based on a dose which did not by itself produce lung leak. We found that PMN were sequestered in the lung after LPS administration, either with or without previous I/R insult. Lung injury was not seen after I/R or LPS alone but was caused by the sequential insults. Finally, there was a 39% mortality in the sequential insult group, compared with $\leqslant 4\%$ morality in all other study groups (fig. 2) [70]. In summary, a relatively brief period of splanchnic I/R appeared to prime the inflammatory response such that low dose LPS exposure during the vulnerable period activated the system, resulting in distant organ injury. Furthermore, splanchnic I/R promoted PMN sequestration in the lung, and the arrival of PMN correlated temporally with progressive endothelial dysfunction. Conversely, the mere presence of increased numbers of PMN (after LPS alone) was insufficient to produce lung injury.

Our hypothesis then became that splanchnic I/R provokes distal organ injury via a mechanism involving priming of circulating PMN in the reperfused splanchnic bed. Priming was measured as O_2^- generation stimulated by low dose formyl-methionyl-leucyl-phenylalanine (fMLP 10^{-6} mol litre^{-1}). In our I/R model, we had noted that circulating PMN become primed at 2 h of reperfusion [66]. To determine whether priming occurred in the splanchnic circulation, we measured priming of PMN drawn from the splanchnic inflow (aorta) as well as the splanchnic outflow (portal vein) after 90 min of reperfusion. We found primed PMN in the portal vein but not the aorta (fig. 3) [44]. Around this time, Johnston and colleagues [61] showed that mediators of gut origin are responsible for I/R-induced injury, and that bypassing the liver has no effect on the injury.

Our next series of studies focused on the mechanism of PMN priming in the splanchnic circulation. Although we had not found evidence of bacterial translocation in our severely injured patients who developed MOF [90], we were interested in whether LPS was involved in PMN priming in our I/R model. We measured LPS levels in the plasma of laparotomized rodents *vs* those subjected to splanchnic I/R, and found no difference. In addition, elimination of LPS by E5 monoclonal antibody had no effect on PMN priming after I/R [69]. As we had previously suspected, something other than LPS is responsible for PMN priming and activation after splanchnic I/R. We began our search for inflammatory mediators capable of PMN priming, which were generated in the gut.

Gut-derived mediators of neutrophil priming

Although numerous inflammatory mediators have been identified as contributors to SIRS and MOF, our investigations have identified two particular compounds as relevant gut-derived mediators of PMN priming: PAF and IL-6.

PLATELET-ACTIVATING FACTOR

Platelet-activating factor (PAF) is a biologically active phospholipid which is synthesized *de novo* continuously, but which may be generated to a greater degree via remodelling of membrane-bound lipids. Phospholipases catalyse the splitting of membrane phospholipids. Phospholipidase A_2 (PLA_2) is designated as such because it cleaves the fatty acid (Acyl) group from the middle (sn-2) carbon of the phospholipid's glycerol backbone [4]. If the sn-2 acyl group is arachidonate, eiconsanoid synthesis is initiated. When the remaining phospholipid has an *O*-alkyl ether in the sn-1 position and a phosphocholine moiety in the sn-3 position, lyso-PAF is formed and PAF synthesis is initiated by a calcium-dependent acetyltransferase. PLA_2 can be activated by ROM [29]; in addition, ROM inhibit PAF acetylhydrolase, the enzyme that catabolises PAF [3]. Given the high concentration of PLA_2 in intestinal mucosa, PLA_2 activation and subsequent PAF formation are a likely consequence of splanchnic I/R [4, 101].

PAF has many known pro-inflammatory effects, including PMN priming and PMN-endothelial adherence [7, 47, 58, 87, 111, 131]. Few clinical studies have actually documented increases in PAF concentrations after injury, in part because of the inherent logistic difficulties in its detection and quantitation. Nevertheless, there is compelling evidence involving PAF in postinjury hyperinflammation [24, 93. 106, 123, 124]. Furthermore, I/R-induced PMN adherence to endothelium can be

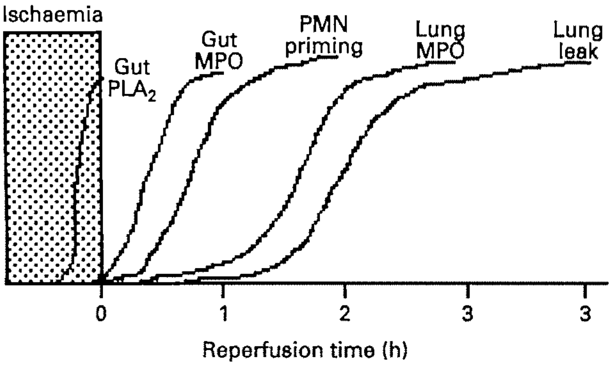

Figure 4 Temporal sequence of events pertinent to the pathophysiology of splanchnic I/R-induced distant organ injury, based on studies from our laboratory. Activation of intestinal phospholipase A_2 (PLA_2) during ischaemia is a proximal event; accumulation of polymorphonuclear leucocytes (PMN) in the gut precedes recovery of primed PMN from the circulation. PMN are sequestered in the lung, and then lung leak is noted. MPO = myeloperoxidase.

diminished by PAF-receptor antagonists [110, 135]. Our finding that PAF was responsible for PMN priming in patients after both thermal and mechanical trauma [106] prompted a series of laboratory investigations. Activation of gut PLA_2 was temporally correlated with PMN priming in our rodent mesenteric I/R model (fig. 4); inhibition of PLA_2 was protective against distant organ injury [68]. We subsequently confirmed PAF production in the distal small bowel after gut I/R, and a PAF-receptor antagonist inhibited PMN priming in this setting [63].

INTERLEUKIN 6

Interleukin 6 (IL-6) is considered an integral mediator of the physiological acute phase response to injury [27]; however, excessive and prolonged elevations of circulating IL-6 concentrations in patients after trauma, burns and elective surgery are associated with morbidity and mortality [9, 33, 39, 41, 85, 114]. The precise role of IL-6 in mediating adverse post-injury events remains ill-defined; moreover, the specific source and stimuli of IL-6 are not entirely clear. IL-6 is inducible in nearly every human tissue and cell type; numerous cytokines, growth factors, hormones, neuropeptides, leukotrienes and microbial products stimulate its production. The short half-life of IL-6 in serum (less than 1 h) combined with the fact that IL-6 is constantly detected in blood, suggests continuous production of IL-6. An intestinal source of IL-6 after surgery and trauma has been suggested. Baigrie and colleagues [10] found significantly higher elevations of IL-6 in inferior mesenteric veins than systemic veins during and after aortic cross-clamping in aortic surgery. Similarly, Wortel and colleagues [134] detected IL-6 in higher concentrations in portal *vs* peripheral venous blood in patients after pancreatic and hepatic resolutions. Deitch and colleagues [36] found higher IL-6 concentrations in portal *vs* cardiac blood after haemorrhagic shock in rats. Thus, IL-6 appears to be generated in the gut after systemic insults. In fact, Meyer and colleagues [86] have demonstrated IL-6 production in intestinal mucosa *in vivo*.

IL-6 is capable of promoting hyperinflammation and organ injury. It increases endothelial permeability in the absence of PMN [78]. In addition, accumulating evidence suggests that IL-6 mediates inflammation by modulating the functional repertoire of the mature PMN. Circumstantial evidence comes from a recent study showing coordinate increases in circulating concentrations of IL-6 and PMN elastase after aortic cross-clamping [62], raising the possibility that IL-6 may be involved in reperfusion injury. Oka and colleagues [100] demonstrated that patients with postoperative complications had higher concentrations of IL-6 than those without complications; furthermore, PMN priming for release of elastase was also higher in the cohort with complications. Redmond and colleagues [112] demonstrated that open cholecystectomy patients, shown to have higher IL-6 concentrations, had increased PMN chemotaxis and priming for O_2^- release compared with laparoscopic cholecystectomy patients. In addition, the open cholecystectomy group had more septic complications. We have studied the effects of IL-6 on PMN cytotoxic functions *in vitro*, and found that IL-6 can sensitize PMN to the effects of a subsequent inflammatory mediator [20]. IL-6 by itself does not prime PMN for O_2^- release; however, when quiescent PMN are incubated with IL-6 and then exposed to PAF, the PMN are primed for O_2^- release. The concentration of PAF required for this effect is 100-fold lower than that required to prime PMN without prior IL-6 stimulation. Mullen and colleagues [94] have similarly demonstrated synergy between IL-6 and TNF-α in PMN priming. IL-6 may also affect PMN-mediated inflammation by modulating apoptosis, or programmed cell death. PMN flux into the interstitial space is unidirectional, and PMN must meet their fate *in situ*. The physiological mechanism of obligatory PMN clearance is believed to be apoptosis. Senescent, apoptotic PMN initiate a signal prompting macrophage phagocytosis. This cytophagocytosis resolves inflammation without activation of the macrophage or exocytosis of cytotoxic PMN contents. Recently, this process has been identified as an important mechanism in the normal resolution of inflammatory processes and the limitation of inflammatory tissue injury. We have found that IL-6 delays PMN apoptosis, resulting in a larger population of non-apoptotic (surviving) PMN with a greater collective capacity for O_2^- production than untreated PMN [18]. The IL-6-mediated delay of PMN apoptosis could postpone the clearance of PMN from a site of inflammation, prolong release of ROM and proteolytic enzymes and aggravate PMN-mediated tissue injury and organ failure.

Although a direct causal link has not been made between IL-6 and MOF, there is an increasing body of evidence suggesting IL-6 is a pivotal component of the hyperinflammatory cytokine cascade driving SIRS. Simms and colleagues [119] studied patients with SIRS, and found that PMN had upregulated functions during SIRS; this upregulation persisted in patients who developed MOF but not in those who did not develop MOF. An anti-IL-6 antibody was effective in reducing PMN oxidative responses, implicating IL-6 as the primary PMN stimulant in the circulation. Gennari and colleagues [48] demonstrated that IL-6 neutralization decreased IL-6 concentrations and bacterial translocation, and improved bacterial killing; in addition, a correlation between IL-6 concentrations and survival time was observed.

While other cytokines (e.g. TNF and IL-1) may also be generated in the gut, IL-6 has been the one most consistently associated with adverse clinical outcomes. For example, we measured IL-6 and TNF concentrations in patients sustaining major trauma [90]. IL-6 concentrations were elevated immediately after injury, but TNF concentrations were not higher than uninjured controls at any time. Hoch and colleagues [57] found elevations of IL-6 and IL-8 in proportion to the severity of injury in trauma patients, but detected no endotoxin or IL-1α, and no elevations of TNF-α. Meade and colleagues [83] similarly found elevated concentrations of IL-6 and IL-8 after injury, but could not detect IL-1β, TNF-α or endotoxin at any time. In this study, both IL-6 and IL-8 concentrations remained elevated for more prolonged periods in patients who developed ARDS. In patients undergoing elective surgery, DiPadova and colleagues [37] found early increases in IL-6 after surgery, but did not see increases in IL-1 or TNF. In an animal model of I/R injury, Cipolle and colleagues [31] found IL-6 but not TNF after reperfusion. Marty and colleagues [77] showed that IL-6 concentrations were higher in non-survivors than surviving MOF patients, and that IL-6 elevations were similar in MOF of septic and non-septic origin. In liver transplant patients with MOF and suspected bacterial infections, Rosenbloom and colleagues [113] found IL-6, but not IL-1β or TNF, to correlate with organ failure.

Thus, there is a great deal of evidence for the critical involvement of IL-6 in hyperinflammation after injury. IL-6 appears to exert its effects via a PAF mechanism [17], and actually stimulates PMN to produce PAF [19]. Clearly, the next step in the study of IL-6 is to attempt to inhibit it in a splanchnic I/R model.

Mechanisms of distant organ injury

Our trauma research centre programme has recently focused on the mechanisms involved in distant organ injury. Presuming primed PMN exiting the splanchnic circulation are the mediators of distant organ injury, we have been interested in the interactions involved in PMN-mediated organ dysfunction. PMN-endothelial interactions are pivotal in tissue injury. Conceptually, there are at least three distinguishable phases of PMN-endothelial interactions, which involve different families of adhesion molecules [26]. The first is a low-affinity process, thought to be mediated by endothelial expression of selections (E, P and L), which produces rolling of PMN along the endothelium. The second phase is high-affinity, firm adhesion of PMN, mediated primarily by intercellular adhesion molecule (ICAM)-1 on the endothelium and the CD11/CD18 (β_2-integrin) complex on the PMN. ICAM-1 is also directly involved in the third phase, transendothelial migration. Blockade of the neutrophil CD11b receptor has been shown to be effective in reducing liver and lung injury after I/R [56, 67]. We have identified ICAM-1 as a pivotal regulator of PMN-mediated cytotoxicity *in vitro* [13], and several investigative groups have demonstrated a role for ICAM-1, in I/R-induced injury [43, 96, 122, 132]. Finally, recent evidence has implicated both IL-6 and PAF in upregulating ICAM-1 after I/R injury [30, 75].

Future directions

The data reviewed here strongly implicate splanchnic I/R in the genesis of malignant hyperinflammation resulting in MOF. The precise mechanistic events and relevant temporal associations remain to be elucidated. Until we develop agents to interfere with the inflammatory cascade, we must focus on prevention and supportive care. The principles of aggressive resuscitation [88], early fracture fixation and tissue debridement [22], and enteral nutritional support with immune-enhancing diets [89] have all been shown to be beneficial in attenuating the inflammatory response and MOF. Resuscitation should be targeted towards augmenting the splanchnic circulation. Recently, Ivatury and colleagues [59] showed that resuscitation of patients to supranormal levels of oxygen delivery and consumption did not consistently normalize gastric mucosal pH; however, when normalization of gastric mucosal pH was used as an endpoint of resuscitation, there was improved survival. This suggests that direct monitoring of the splanchnic circulation is preferable to systemic goal-oriented resuscitation. Low-dose dopexamine may prove a useful adjunct to augment splanchnic perfusion [80]. A final therapeutic intervention that may prove beneficial is the administration of inhaled nitric oxide (NO•). Jacob and colleagues [60] have found that trauma patients have inhibited NO• production. NO• has been used with increasing enthusiasm in the treatment of refractory ARDS [81]. Its ability to selectively vasodilate ventilated segments' of lung improves ventilation: perfusion matching. In addition, NO• has been shown to attenuate I/R-induced lung injury, presumably by inhibiting PMN influx into the lungs [1]. We have shown that NO• reduces endothelial expression of ICAM-1 (unpublished data), providing a potential protective mechanism from I/R-induced lung injury. Thus, interventions to improve splanchnic perfusion in the postinjury period, and to attenuate the systemic inflammatory response to injury, are going to be critical in preventing MOF and improving patient outcome.

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References

1. Abdih H, Kelly CJ, Bouchier-Hayes D, William R, Watson G, Redmond HP, Burke P, Bouchier-Hayes DJ. Nitric oxide (endothelium-derived relaxing factor) attenuates revascularization-induced lung injury. *Journal of Surgical Research* 1994; **57**: 39–43.
2. Adar R, Franklin A, Spark RF, Rosoff CB, Salzman EW. Effect of dehydration and cardiac tamponade on superior mesenteric artery flow: role of vasoactive substances. *Surgery* 1976; **79**: 534–543.
3. Ambrosio G, Oriente A, Napoli C, Palumbo G, Chiariello P, Marone G, Condorelli M, Chiariello M, Triggiani M. Oxygen radicals inhibit human plasma acetylhydrolase, the enzyme that catabolizes platelet-activating factor. *Journal of Clinical Investigation* 1994; **93**: 2408–2416.
4. Anderson BO, Moore EE, Banerjee A. Phospholipase A_2 regulates critical inflammatory mediators of multiple organ failure. *Journal of Surgical Research* 1994; **56**: 199–205.
5. Anderson BO, Moore EE, Moore FA, Leff JA, Terada LS, Harken AH, Repine JE. Hypovolemic shock promotes neutrophil sequestration in lungs by a xanthine oxidase-related mechanism. *Journal of Applied Physiology* 1991; **71**: 1862–1865.
6. Anner H, Kaufman RP jr, Kobzik L, Valeri CR, Shepro D, Hechtman HB. Pulmonary hypertension and leukosequestration after lower torso ischemia. *Annals of Surgery* 1987; **206**: 642–648.
7. Arnould T, Michiels C, Remacle J. Increased PMN adherence on endothelial cells after hypoxia: involvement of PAF, CD18/CD11b, and ICAM-1. *American Journal of Physiology* 1993; **264**: C1102–C1110.
8. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–323.
9. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *British Journal of Surgery* 1992; **79**: 757–760.
10. Baigrie RJ, Lamont PM, Whiting S, Morris PJ. Portal endotoxin and cytokine responses during abdominal aortic surgery. *American Journal of Surgery* 1993; **166**: 248–251.
11. Bailey RW, Bulkley GB, Hamilton SR, Morris JB, Haglund UH. Protection of the small intestine from nonocclusive mesenteric ischemic injury due to cardiogenic shock. *American Journal of Surgery* 1987; **153**: 108–116.
12. Baker JW, Deitch EA, Li M, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. *Journal of Trauma* 1988; **28**: 896–906.
13. Barnett CC jr, Moore EE, Moore FA, Biffl WL, Smith MR jr, Carl VS. Intercellular adhesion molecule-1 promotes neutrophil-mediated cytotoxicity. *Surgery* 1995; **118**: 171–176.
14. Batelli MG. Enzymic conversion of rat liver xanthine oxidase from dehydrogenase (D form) to oxidase (O form). *FEBS Letters* 1980; **113**: 47–51.
15. Baue AE. Multiple, progressive, or sequential systems failure: a syndrome of the 1970s. *Archives of Surgery* 1975; **110**: 779–781.
16. Baue AE. The horror autotoxicus and multiple organ failure. *Archives of Surgery* 1992; **127**: 1451–1462.
17. Biffl WL, Moore EE, Moore FA, Barnett CC jr. Interleukin-6 delays neutrophil apoptosis via a mechanism involving platelet-activating factor. *Journal of Trauma* 1994; **40**: 575–579.
18. Biffl WL, Moore EE, Moore FA, Barnett CC jr, Carl VS, Peterson VM. Interleukin-6 delays neutrophil apoptosis. *Archives of Surgery* 1996; **113**: 24–30.
19. Biffl WL, Moore EE, Moore FA, Barnett CC jr, Silliman CC, Peterson VM. Interleukin-6 stimulates neutrophil production of platelet-activating factor. *Journal of Leukocyte Biology* 1996; (in press).
20. Biffl WL, Moore EE, Moore FA, Carl VS, Kim FJ, Franciose RJ. Interleukin-6 potentiates neutrophil priming with platelet-activating factor. *Archives of Surgery* 1994; **129**: 1131–1136.
21. Blalock A. Acute circulatory factor as exemplified by shock and haemorrhage. *Surgery Gynecology and Obstetrics* 1934; **58**: 551–566.
22. Border JR, Hassett J, LaDuca J, Seibel R, Steinberg S, Mills B, Losi P, Border D. The gut origin septic states in blunt multiple trauma (ISS = 40) in the ICU. *Annals of Surgery* 1987; **206**: 427–448.
23. Botha AJ, Moore FA, Moore EE, Fontes B, Banerjee A, Peterson VM. Postinjury neutrophil priming and activation states: therapeutic challenges. *Shock* 1995; **3**: 157–166.
24. Botha AJ, Moore FA, Moore EE, Peterson VM. Early neutrophil priming for superoxide release after injury is via a platelet activating factor mechanism. *British Journal of Surgery* 1995; **82**: 686.
25. Cambria RA, Anderson RJ, Dikdan G, Teehan EP, Hernandez-Maldonado JJ, Hobson RW II. Leukocyte activation is ischemia-reperfusion injury of skeletal muscle. *Journal of Surgical Research* 1991; **51**: 13–17.
26. Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. *Blood* 1994; **84**: 2068–2101.
27. Castell JV, Gomez-Lechon MJ, David M, Andus T, Geiger T, Trullenque R, Fabra R, Heinrich PC. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Letters* 1989; **242**: 237–239.
28. Cerra FB, Maddaus MA, Dunn DL, Wells CL, Konstantinides NN, Lehmann SL, Mann HJ. Selective gut decontamination reduces nosocomial infections and length of stay but not mortality or organ failure in surgical intensive care unit patients. *Archives of Surgery* 1992; **127**: 163–169.
29. Chakraborti S, Gurtner GH, Michael JR. Oxidant-mediated activation of phospholipase A_2 in pulmonary endothelium. *American Journal of Physiology* 1989; **257**: L430–L437.
30. Chihara J, Maruyama I, Yasuba H, Yasukawa A, Yamamoto T, Kurachi D, Mouri T, Seguchi M, Nakajima S. Possible induction of intercellular adhesion molecule-1 expression on endothelial cells by platelet-activating factor. *Journal of Lipid Mediators* 1992; **5**: 159–162.
31. Cipolle MD, Pasquale MD, Shearer J, Caldwell M, Cerra F. Blunt injury augments interleukin-6 but not tumor necrosis factor in isolated, perfused rat hindlimbs. *Journal of Trauma* 1994; **37**: 91–99.
32. Consensus Conference. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Critical Care Medicine* 1992; **20**: 864–874.
33. Damas P, Ledoux D, Nys M, Vrindts Y, De Groote D, Franchimont P, Lamy M. Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Annals of Surgery* 1992; **215**: 356–362.
34. Dantzker DR. The gastrointestinal tract: the canary of the body? *Journal of the American Medical Association* 1993; **270**: 1247–1248.
35. Deitch EA, Bridges RM. Effect of stress and trauma on bacterial translocation from the gut. *Journal of Surgical Research* 1987; **42**: 536–542.
36. Deitch EA, Xu D, Franko L, Ayala A, Chaudry IH. Evidence favoring the role of the gut as a cytokine-generating organ in rats subjected to hemorrhagic shock. *Shock* 1994; **1**: 141–146.
37. DiPadova F, Pozzi C, Tondre MJ, Tritapepe R. Selective and early increase of IL-1 inhibitors, IL-6 and cortisol after elective surgery. *Clinical and Experimental Immunology* 1991; **85**: 137–142.
38. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19**: 1037–1040.
39. Drost AC, Burleson DG, Cioffi WG jr, Mason AD jr, Pruitt BA jr. Plasma cytokines after thermal injury and their relationship to infection. *Annals of Surgery* 1993; **218**: 74–78.
40. Eiseman B, Beart R, Norton L. Multiple organ failure. *Surgery Gynecology and Obstetrics* 1977; **144**: 323–326.
41. Ertel W, Faist E, Nestle C, Hueltner L, Storck M, Schildberg FW. Kinetics of interleukin-2 and interleukin-6 synthesis following major mechanical trauma. *Journal of Surgical Research* 1990; **48**: 622–628.
42. Faist E, Baue AE, Dittmer H, Heberer G. Multiple organ failure in polytrauma patients. *Journal of Trauma* 1983; **23**: 775–787.
43. Farhood A, McGuire GM, Manning AM, Miyasaka M,

Smith CW, Jaeschke H. Intercellular adhesion molecule 1 expression and its role in neutrophil-induced ischemia-reperfusion injury in rat liver. *Journal of Leukocyte Biology* 1995; **57**: 368–374.

44. Franciose RJ, Moore EE, Moore FA, Koike K, Carl VS, Banerjee A. Postischemic gut is the priming bed for PMNs. *Surgical Forum* 1993; **XLIV**: 142–144.
45. Freischlag JA, Hanna D. Neutrophil phagocytosis and chemotaxis after reperfusion injury. *Journal of Surgical Research* 1992; **52**: 152–156.
46. Fry DE, Pearlstein L, Fulton RL, Polk HC jr. Multiple system organ failure: the role of uncontrolled infection. *Archives of Surgery* 1980; **115**: 136–140.
47. Gay JC, Beckman JK, Zaboy KA, Lukens JN. Modulation of neutrophil oxidative responses to soluble stimuli by platelet-activating factor. *Blood* 1986; **67**: 931–936.
48. Gennari R, Alexander JW, Pyles T, Hartmann S, Ogle CK. Effects of antimurine interleukin-6 on bacterial translocation during gut-derived sepsis. *Archives of Surgery* 1994; **129**: 1191–1197.
49. Goldman G, Welbourn R, Klausner JM, Paterson IS, Kobzik L, Valeri CR, Shepro D, Hechtman HB. Ischemia activates neutrophils but inhibits their local and remote diapedesis. *Annals of Surgery* 1990; **211**: 196–201.
50. Goris RJA, Boekhorst TPAT, Nuytinck JKS, Gimbrere JSF. Multiple-organ failure: generalized autodestructive inflammation? *Archives of Surgery* 1985; **120**: 1109–1115.
51. Goris RJA, van Bebber IPT, Mollen RMH, Koopman JP. Does selective decontamination of the gastrointestinal tract prevent multiple organ failure? *Archives of Surgery* 1991; **126**: 561–565.
52. Granger DN. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. *American Journal of Physiology* 1988; **255**: H1269–H1275.
53. Granger DN, Benoit JN, Suzuki M, Grisham MB. Leukocyte adherence to venular endothelium during ischemia-reperfusion. *American Journal of Physiology* 1989; **257**: G683–G688.
54. Grisham MB, Hernandez LA, Granger DN. Xanthine oxidase and neutrophil infiltration in intestinal ischemia. *American Journal of Physiology* 1986; **251**: G567–G574.
55. Hernandez LA, Grisham MB, Twohig B, Arfors KE, Harlan JM, Granger DN. Role of neutrophils in ischemia-reperfusion-induced microvascular injury. *American Journal of Physiology* 1987; **253**: H699–H703.
56. Hill J, Lindsay T, Rusche J, Valeri CR, Shepro D, Hechtman HB. A Mac-1 antibody reduces liver and lung injury but not neutrophil sequestration after intestinal ischemia-reperfusion. *Surgery* 1992; **112**: 166–172.
57. Hoch RC, Rodriguez R, Manning T, Bishop M, Mead P, Shoemaker WC, Abraham E. Effects of accidental trauma on cytokine and endotoxin production. *Critical Care Medicine* 1993; **21**: 839–845.
58. Ingraham LM, Coates TD, Allen JM, Higgins CP, Baehner RL, Boxer LA. Metabolic, membrane, and functional responses of human polymorphonuclear leukocytes to platelet-activating factor. *Blood* 1982; **59**: 1259–1266.
59. Ivatury RR, Simon RJ, Havriliak D, Garcia C, Greenbarg J, Stahl WM. Gastric mucosal pH and oxygen delivery and oxygen consumption indices in the assessment of adequacy of resuscitation after trauma: a prospective, randomized study. *Journal of Trauma* 1995; **39**: 128–136.
60. Jacob TD, Ochoa JB, Udekwu AO, Wilkinson J, Murray T, Billiar TR, Simmons RL, Marion DW, Peitzman AB. Nitric oxide production is inhibited in trauma patients. *Journal of Trauma* 1993; **35**: 590–597.
61. Johnston TD, Fischer R, Chen Y, Reed RL II. Lung injury from gut ischemia: insensitivity to portal blood flow diversion. *Journal of Trauma* 1993; **35**: 508–511.
62. Kawamura T, Wakusawa R, Okada K, Inada S. Elevation of cytokines during open heart surgery with cardiopulmonary bypass: participation of interleukin 8 and 6 in reperfusion injury. *Canadian Journal of Anaesthesia* 1993; **40**: 1016–1021.
63. Kim FJ, Moore EE, Moore FA, Biffl WL, Fontes B, Banerjee A. Reperfused gut elaborates PAF that chemoattracts and primes neutrophils. *Journal of Surgical Research* 1995; **58**: 636–640.
64. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. *Annals of Surgery* 1985; **202**: 685–693.
65. Knaus WA, Wagner DP. Multiple systems organ failure: epidemiology and prognosis. *Critical Care Clinics of North America* 1989; **5**: 221–232.
66. Koike K, Moore EE, Moore FA, Carl VS, Pitman JM, Banerjee A. Phospholipase A_2 inhibition decouples lung injury from gut ischemia-reperfusion. *Surgery* 1992; **112**: 173–180.
67. Koike K, Moore EE, Moore FA, Franciose RJ, Fontes B, Kim FJ. CD11b blockade prevents lung injury despite neutrophil priming after gut ischemia/reperfusion. *Journal of Trauma* 1995; **39**: 23–28.
68. Koike K, Moore EE, Moore FA, Kim FJ, Carl VS, Banerjee A. Gut phospholipase A_2 mediates neutrophil priming and lung injury after mesenteric ischemia-reperfusion. *American Journal of Physiology* 1995; **268**: G397–G403.
69. Koike K, Moore EE, Moore FA, Read RA, Carl VS, Banerjee A. Gut ischemia/reperfusion produces lung injury independent of endotoxin. *Critical Care Medicine* 1994; **22**: 1438–1444.
70. Koike K, Moore FA, Moore EE, Poggetti RS, Tuder RM, Banerjee A. Endotoxin after gut ischemia/reperfusion causes irreversible lung injury. *Journal of Surgical Research* 1992; **52**: 656–662.
71. Koike K, Moore FA, Moore EE, Read RA, Carl VS, Banerjee A. Gut ischemia mediates lung injury by a xanthine oxidase-dependent neutrophil mechanism. *Journal of Surgical Research* 1993; **54**: 469–473.
72. Korthuis RJ, Smith JK, Carden DL. Hypoxic reperfusion attenuates postischemic microvascular injury. *American Journal of Physiology* 1989; **256**: H315–H319.
73. Koziol JM, Rush BF jr, Smith SM, Machiedo GW. Occurrence of bacteremia during and after hemorrhagic shock. *Journal of Trauma* 1988; **28**: 10–16.
74. Kubes P. Ischemia-reperfusion in feline small intestine: a role for nitric oxide. *American Journal of Physiology* 1993; **264**: G143–G149.
75. Kukielka GL, Youker KA, Hawkins HK, Perrard JL, Michael LH, Ballantyne CM, Smith CW, Entman ML. Regulation of ICAM-1 and IL-6 in myocardial ischemia: effect of reperfusion. *Annals of the New York Academy of Sciences* 1994; **574**: 258–270.
76. Marshall JC, Christou NV, Horn R, Meakins JL. The microbiology of multiple organ failure: the proximal gastrointestinal tract as an occult reservoir of pathogens. *Archives of Surgery* 1988; **123**: 309–315.
77. Marty C, Misset B, Tamion F, Fitting C, Carlet J, Cavaillon J-M. Circulating interleukin-8 concentrations in patients with multiple organ failure of septic and nonseptic origin. *Critical Care Medicine* 1994; **22**: 673–679.
78. Maruo N, Morita I, Shirao M, Murota S-I. IL-6 increases endothelial permeability in vitro. *Endocrinology* 1992; **131**: 710–714.
79. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *Journal of the American Medical Association* 1993; **270**: 1203–1210.
80. Maynard ND, Bihari DJ, Dalton RN, Smithies MN, Mason RC. Increasing splanchnic blood flow in the critically ill. *Chest* 1995; **108**: 1648–1654.
81. McIntyre RC jr, Moore FA, Moore EE, Piedalue F, Haenel JS, Fullerton DA. Inhaled nitric oxide variably improves oxygenation and pulmonary hypertension in patients with acute respiratory distress syndrome. *Journal of Trauma* 1995; **39**: 418–425.
82. McNeill JR, Stark RD, Greenway CV. Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. *American Journal of Physiology* 1970; **219**: 1342–1347.
83. Meade P, Shoemaker WC, Donnelly TJ, Abraham E, Jagels MA, Cryer HG, Hugli TE, Bishop MH, Wo CCJ. Temporal patterns of hemodynamics, oxygen transport, cytokine activity, and complement activity in the development of adult respiratory distress syndrome after severe injury. *Journal of Trauma* 1994; **36**: 651–657.
84. Meakins JL, Marshall JC. The gastrointestinal tract: the 'motor' of MOF. *Archives of Surgery* 1986; **121**: 197–201.

85. Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, Leeper K. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS: plasma IL-1β and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995; **107**: 1062–1073.
86. Meyer TA, Wang J, Tiao GM, Ogle CK, Fischer JE, Hasselgren P-O. Sepsis and endotoxemia stimulate intestinal interleukin-6 production. *Surgery* 1995; **118**: 336–342.
87. Milhoan KA, Lane TA, Bloor CM. Hypoxia induces endothelial cells to increase their adherence for neutrophils: role of PAF. *American Journal of Physiology* 1992; **263**: H956–H962.
88. Moore FA, Haenel JB, Moore EE, Whitehill TA. Incommensurate oxygen consumption in response to maximal oxygen availability predicts postinjury multiple organ failure. *Journal of Trauma* 1992; **33**: 58–67.
89. Moore FA, Moore EE, Kudsk KA, Brown RO, Bower RH, Koruda MJ, Baker CC, Barbul A. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. *Journal of Trauma* 1994; **37**: 607–615.
90. Moore FA, Moore EE, Poggetti R, McAnena OJ, Peterson VM, Abernathy CM, Parsons PE. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. *Journal of Trauma* 1991; **31**: 629–638.
91. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure—a bimodal phenomenon. *Journal of Trauma* 1996; (in press).
92. Morales J, Kibsey P, Thomas PD, Poznansky MJ, Hamilton SM. The effects of ischemia and ischemia-reperfusion on bacterial translocation, lipid peroxidation, and gut histology: studies on hemorrhagic shock in pigs. *Journal of Trauma* 1992; **33**: 221–227.
93. Mozes T, Braquet P, Filep J. Platelet-activating factor: an endogenous mediator of mesenteric ischemia-reperfusion-induced shock. *American Journal of Physiology* 1989; **257**: R872–R877.
94. Mullen PG, Windsor ACJ, Walsh CJ, Fowler AA III, Sugerman HJ. Tumor necrosis factor-α and interleukin-6 selectively regulate neutrophil function in vitro. *Journal of Surgical Research* 1995; **58**: 124–130.
95. Munster AM, Smith-Meek M, Dickerson C, Winchurch RA. Translocation: incidental phenomenon or true pathology? *Annals of Surgery* 1993; **218**: 321–327.
96. Nakano H, Kuzume M, Namatame K, Yamaguchi M, Kumada K. Efficacy of intraportal injection of anti-ICAM-1 monoclonal antibody against liver cell injury following warm ischemia in the rat. *American Journal of Surgery* 1995; **170**: 64–66.
97. Nilddon UA, Lundgren O, Haglund U. Radical production during intestinal ischemia and reperfusion in vivo in the cat—an ESR study. In: Simic M, ed. *Proceedings of 4th International Congress on Oxygen Radicals*, 1987: 150–152.
98. Norton LW. Does drainage of intraabdominal pus reverse multiple organ failure? *American Journal of Surgery* 1985; **149**: 347–350.
99. Nuytinck HKS, Offermans XJMW, Kubat K, Goris RJA. Whole-body inflammation in trauma patients: an autopsy study. *Archives of Surgery* 1988; **123**: 1519–1524.
100. Oka Y, Murata A, Nishijima J, Yasuda T, Hiraoka N, Ohmachi Y, Yasuda T, Kitagawa K, Toda H, Tanaka N, Ogawa M, Mori T. Enhanced attachment and elastase-releasing capacity of neutrophils after surgery. *American Journal of Surgery* 1994; **167**: 405–511.
101. Otamiri T, Lindahl M, Tagesson C. Phospholipase A_2 inhibition prevents mucosal damage associated with small intestinal ischaemia in rats. *Gut* 1988; **29**: 489–494.
102. Parks DA, Granger DN. Contributions of ischemia and reperfusion to mucosal lesion formation. *American Journal of Physiology* 1986; **250**: G749–G753.
103. Patel A, Kaleya RN, Sammartano RJ. Pathophysiology of mesenteric ischemia. *Surgical Clinics of North America* 1992; **72**: 31–41.
104. Peitzman AB, Udekwu AO, Ochoa J, Smith S. Bacterial translocation in trauma patients. *Journal of Trauma* 1991; **31**: 1083–1087.
105. Perry MA, Wadhwa SS. Gradual reintroduction of oxygen reduces reperfusion injury in cat stomach. *American Journal of Physiology* 1988; **254**: G366–G372.
106. Pitman JM III, Thurman GW, Anderson BO, Poggetti RS, Nelson DW, Hartford CE, Peterson VM, Ketch LL, Moore EE, Harken AH, Ambruso DR. Platelet-activating factor may mediate neutrophil priming following clinical burn or blunt trauma. *Surgical Forum* 1989; **XL**: 108–109.
107. Poggetti RS, Moore FA, Moore EE, Bensard DD, Anderson BO, Banerjee A. Liver injury is a reversible neutrophil-mediated event following gut ischemia. *Archives of Surgery* 1992; **127**: 175–179.
108. Poggetti RS, Moore FA, Moore EE, Koike K, Banerjee A. Simultaneous liver and lung injury following gut ischemia is mediated by xanthine oxidase. *Journal of Trauma* 1992; **32**: 723–728.
109. Polk HC jr, Shields CL. Remote organ failure: a valid sign of occult intra-abdominal infection. *Surgery* 1977; **81**: 310–313.
110. Rainger GE, Fisher A, Shearman C, Nash GB. Adhesion of flowing neutrophils to cultured endothelial cells after hypoxia and reoxygenation in vitro. *American Journal of Physiology* 1995; **269**: H1398–H1406.
111. Read RA, Moore EE, Moore FA, Carl VS, Banerjee A. Platelet-activating factor-induced polymorphonuclear neutrophil priming independent of $CD11_B$ adhesion. *Surgery* 1993; **114**: 308–313.
112. Redmond HP, Watson RWG, Houghton T, Condron C, Watson RGK, Bouchier-Hayes D. Immune function in patients undergoing open vs laparoscopic cholecystectomy. *Archives of Surgery* 1994; **129**: 1240–1246.
113. Rosenbloom AJ, Pinsky MR, Bryant JL, Shin A, Tran T, Whiteside T. Leukocyte activation in the peripheral blood of patients with cirrhosis of the liver and SIRS: correlation with serum interleukin-6 levels and organ dysfunction. *Journal of the American Medical Association* 1995; **274**: 58–65.
114. Roumen RMH, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GAP, Sauerwein RW, van der Meer JWM, Goris RJA. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma: relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Annals of Surgery* 1993; **218**: 769–776.
115. Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA. Pneumonia: cause or symptom of postinjury multiple organ failure? *American Journal of Surgery* 1993; **166**: 606–611.
116. Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Early predictors of postinjury multiple organ failure. *Archives of Surgery* 1994; **129**: 39–45.
117. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. *Journal of Trauma* 1995; **38**: 185–193.
118. Schmeling DJ, Caty MG, Oldham KT, Guice KS, Hinshaw DB. Evidence for neutrophil-related acute lung injury after intestinal ischemia-reperfusion. *Surgery* 1989; **106**: 195–202.
119. Simms HH, D'Amico R. Polymorphonuclear leukocyte dysregulation during the systemic inflammatory response syndrome. *Blood* 1994; **83**: 1398–1407.
120. Sori AJ, Rush BF jr, Lysz TW, Smith S, Machiedo GW. The gut as source of sepsis after hemorrhagic shock. *American Journal of Surgery* 1988; **155**: 187–192.
121. Southorn PA, Powis G. Free radicals in medicine. I. Chemical nature and biologic reactions. *Mayo Clinic Proceedings* 1988; **63**: 381–389.
122. Squadrito F, Altavilla D, Canale P, Ioculano M, Campo GM, Ammendolia L, Squadrito G, Saitta A, Calapai G, Caputi AP. Contribution of intercellular adhesion molecule 1 to the pathogenesis of splanchnic artery occlusion shock in the rat. *British Journal of Pharmacology* 1994; **113**: 912–916.
123. Stahl GL, Bitterman H, Lefer AM. Protective effects of a specific platelet activating factor antagonist, WEB 1086, in traumatic shock. *Thrombosis Research* 1989; **53**: 327–338.
124. Stahl GL, Craft DV, Lento PH, Lefer AM. Detection of platelet-activating factor during traumatic shock. *Circulatory Shock* 1988; **26**: 237–244.
125. Suzuki M, Inauen W, Kvietys PR, Grisham MB, Meininger C, Schelling ME, Granger HJ, Granger DN. Superoxide mediates reperfusion-induced leukocyte-endothelial cell interactions. *American Journal of Physiology* 1989; **257**: H1740–H1745.
126. Tate RM, Repine JE. Neutrophils and the adult respiratory

distress syndrome. *American Review of Respiratory Diseases* 1983; **128**: 552–559.

127. Teschan PE, Post RS, Smith LH jr, Abernathy RS, Davis JH, Gray DM, Howard JM, Johnson KE, Klopp E, Mundy RL, O'Meara MP, Rush BF jr. Post-traumatic renal insufficiency in military casualties. I. Clinical characteristics. In: Howard JM, ed. *Battle casualties in Korea: Studies of the surgical research team. Vol. IV. Post-traumatic renal insufficiency*. 1995: 7–22.
128. Tilney NL, Bailey GL, Morgan AP. Sequential system failure after rupture of abdominal aortic aneurysms: an unsolved problem in postoperative care. *Annals of Surgery* 1973; **178**: 117–122.
129. Turrens JF, Giulivi C, Pinus C. Low level chemiluminescence from isolated hepatocytes, intact lung and intestine in situ. In: Simic M, ed. *Proceedings of 4th International Congress on Oxygen Radicals*. 1987: 64–65.
130. Vedder NB, Fouty BW, Winn RK, Harlan JM, Rice CL. Role of neutrophils in generalized reperfusion injury associated with resuscitation from shock. *Surgery* 1989; **106**: 509–516.
131. Vercellotti GM, Yin HQ, Gustafson KS, Nelson RD, Jacob HS. Platelet-activating factor primes neutrophil responses to agonists: role in promoting neutrophil-mediated endothelial damage. *Blood* 1988; **71**: 1100–1107.
132. Vollmar B, Glasz J, Menger MD, Messmer K. Leukocytes contribute to hepatic ischemia/reperfusion injury via intercellular adhesion molecule-1-mediated venular adherence. *Surgery* 1995; **117**: 15–200.
133. Weiland JE, Davis WB, Holter JF, Mohammed JR, Dorinsky PM, Gadek JE. Lung neutrophils in the adult respiratory distress syndrome: clinical and pathophysiologic significance. *American Review of Respiratory Diseases* 1986; **133**: 218–225.
134. Wortel CH, van Deventer SJH, Aarden LA, Lygidakis NJ, Buller HR, Hoek FJ, Horikx J, ten Cate JW. Interleukin-6 mediates host defence responses induced by abdominal surgery. *Surgery* 1993; **114**: 564–570.
135. Yoshida N, Granger DN, Anderson DC, Rothlein R, Lane C, Kvietys PR. Anoxia/reoxygenation-induced neutrophil adherence to cultured endothelial cells. *American Journal of Physiology* 1992; **262**: H1891–H1898.
136. Zimmerman BJ, Granger DN. Reperfusion injury. *Surgical Clinics of North America* 1992; **72**: 65–83.

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Determinants of intestinal barrier failure in critical illness

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The gut serves not only as a physiological portal for the entry of water and nutrients into the body, but also as a barrier limiting the systemic absorption of intraluminal microbes, microbial products, or both. Evidence exists to support the view that trauma, sepsis or other critical illnesses lead to derangements in the barrier function of the gut. One potential consequence of deranged barrier function is bloodstream invasion by gut-derived pathogens, leading to "primary" bacteraemias or fungaemias, or even metastatic infections.

Another consequence of gut barrier dysfunction might be a several step process leading to a poorly controlled systemic inflammatory response and organ system failure. In the first step of this postulated pathophysiological process, microbes or toxins passively diffuse or are actively transported out of the lumen of the gut into submucosal tissues. In step two, these microbes or toxins activate immune cells in tissues or organs, which are "downstream" from the mucosa (e.g. Kuppfer cells in the liver; macrophages in the lamina propria of the gut, Peyer's patches or mesenteric lymph nodes). In the third step, the activated immune cells release various inflammatory mediators (cytokines, nitric oxide, eicosanoids, platelet activating factor), which have been implicated as being important in the pathogenesis of multiple organ dysfunction. The hypothesis that the gut is an endogenous source of pro-inflammatory agents is attractive because it might explain why signs and symptoms of sepsis, such as fever, leucocytosis, hypermetabolism and organ system dysfunction, frequently are present in critically ill patients, even in the absence of a well-defined focus of infection [42, 91, 92].

Components of the intestinal barrier

Intestinal barrier function depends upon a stratified system of defences. These defences include the normal microbiological flora of the gut, enteric secretions, peristalsis, gut-associated immune cells and the epithelium itself.

Under normal conditions, anaerobic organisms, growing as a carpet on the mucosal surfaces of the gut, limit colonization and overgrowth of other potentially invasive microbes [148]. However, in critically ill patients, possibly because of the administration of broad-spectrum antibiotics, the gut commonly becomes colonized by potentially pathogenic facultative Gram-negative bacilli, Gram-positive cocci and fungi [92, 93]. These organisms are believed to express specialized virulence factors enabling mucosal adherence and penetration [136].

Mucins, secreted by epithelial goblet cells, create a protective viscous gel that hampers bacterial penetration [148]. In addition, active Cl^- transport by epithelial cells promotes intraluminal fluid flux that washes away harmful agents [94]. Upregulation of mucosal Cl^- secretion occurs rapidly after ischaemic [95] or toxic [94] insults, or both, through a host of autocrine, paracrine and, perhaps, hormonal mechanisms. Additionally, mucosal secretions are rich in IgA antibodies that bind and aggregate bacteria [3, 4, 136] and thereby aid in preventing adherence to the mucosa and subsequent trans-epithelial invasion.

As the largest immunological organ of the body, the intestine contains numerous immunoreactive cells, including various subtypes of B- and T-lymphocytes, plasma cells, macrophages, neutrophils, Paneth cells and specialized "M cells" [8, 65]. Together these cells are thought to help prevent systemic infection by lumenally derived invasive microbes. The gut associated lymphoid tissue (GALT) consists of three distinct populations: Peyer's patches, immunocytes within the lamina propria, and interepithelial lymphocytes (IEL).

Found throughout the length of the small intestine, Peyer's patches are mucosal and submucosal lymphoid follicles that are the site of B-cell differentiation and immunoglobulin (IgA) class commitment [8, 65]. A proportion of these B-lymphocytes eventually migrate to the lamina propria, where they are critical in producing IgA that is secreted transcellularly by the epithelial cells. Antigen priming in intestinal lymphoid follicles produces selective humoral responses by stimulating clonal B-cell growth and migration to local as well as systemic sites. This function is facilitated by specialized epithelial cells, termed "M cells" [144], which selectively expose underlying lymphoid aggregates to luminal antigens thereby allowing continuous priming of lymphocytic defences.

IEL and lamina propria lymphocytes are predominately T-cells [8, 21]. These two populations

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differ in phenotype and purpose. IEL predominantly express the CD8 cell surface marker and display cytolytic activity. As the first T-cells exposed to luminal antigens, their defensive role against microbial invasion is an active one. Exposure to infiltrating pathogens triggers both direct cytolytic activity as well as the release of cytokines that stimulate antigen-specific immune responses (IL-5) and epithelial growth (TGF-β). In contrast with IEL, lamina propria T-cells primarily express CD4 antigen and act as facilitators of inflammation and epithelial defences [8]. Activated by specific antigenic recognition, these cells turn on a cascade of protective reactions via cytokines.

The most critical barrier against systemic absorption of intraluminal microbes and microbial products is the epithelium *per se*. Structurally, the intestine is comprised of a single layered columnar epithelium arranged into villus and crypt components. Specialized cell–cell junctional complexes allow for selective paracellular permeability (tight junctions) [83], maintain intercellular adhesion (intermediate junctions and desmosomes) [131] and permit intercellular communication (gap junctions) [166]. The zonula occludens is a circumferential band of apical tight junctions that limits paracellular passage of ions and fluid. Under normal circumstances, tight junctions exclude passive movement of hydrophilic non-charged compounds with a molecular radius > 11.5 Å [83]. Substances that are therefore prevented from paracellular transepithelial movement include lipopolysaccharide (LPS) [149] and a variety of other bacterial-derived proinflammatory substances, such as formyl-methionyl-leucyl-phenylalanine (FMLP) [22] and peptidoglycan-polysaccharides [77], which are present in high concentration within the lumen of the distal small intestine and colon.

Assessment of intestinal mucosal barrier function

In clinical and experimental studies, the integrity of the gut mucosal barrier has been assessed using two very different approaches. One method estimates the degree of transmucosal movement of bacterial or fungal pathogens from the intestinal lumen into the vascular or lymphatic systems, a process referred to as *microbial translocation*. The second method quantitates the *permeability* of the gut to various water-soluble probes.

Microbial translocation does not necessarily imply the loss of epithelial integrity. Under some conditions, translocation in experimental animals subjected to a major stress (e.g. haemorrhage or endotoxaemia) appears to occur via tiny breaks in the continuity of the mucosal epithelial sheet [28, 31]. However, for the most part, translocation is a transcellular rather than a paracellular process [2, 155, 158, 159]. Moreover, in many experimental studies, the extent of translocation is quantitated by enumerating viable colony-forming units (CFU) in mesenteric lymph nodes (MLN) or other organs. However, data using radioactively labelled lumenal bacteria indicate that this approach vastly underestimates the extent of translocation, because most microbes breaching the epithelial barrier are killed [40]. Increases in "translocation" evidenced by increases in CFU in MLN or other organs are predominantly the result of decreased killing rather than increased transepithelial penetration.

Normally, the healthy intestinal mucosa manifests a very low basal level of permeability to large and middle-sized hydrophilic molecules. Systemic uptake of luminally placed water-soluble non-charged compounds such as mono- and disaccharides (e.g. rhamanose and lactulose), radiolabelled organic acid-transition metal complexes (e.g. chromium ehthylenediaminetetra-acetate [^{51}Cr-EDTA]), synthetic polymers (polyethylene glycol) or radiolabelled proteins (albumin) can be used to quantitate the rate of transepithelial flux. In such studies, two probes are commonly employed. One probe (e.g. mannitol) typically consists of a relatively small molecule which permeates moderately well through even normal mucosa. A second probe (e.g. lactulose) consists of a larger molecule, which permeates the normal mucosa only minimally. Probes which are non-metabolisable are chosen, and absorption of the probes is determined by measuring concentrations in plasma or urine. By measuring the *differential* concentrations of two probes, it is possible to remove confounding effects related to changes in intestinal motility (or renal function). Because the zonula occludens restricts intercellular passage of these probes in the luminal as well as vascular direction, permeability can also be assessed in animal models by measuring luminal concentrations of these probes after intravascular administration [35, 59].

Evidence for and against intestinal barrier dysfunction in critically ill humans

Convincing evidence of microbial translocation has been documented in humans under certain conditions. Deitch showed that viable enteric organisms frequently can be isolated from cultures of mesenteric lymph nodes obtained at laparotomy from patients with small bowel obstruction [26]. Similar results were obtained by Ambrose and colleagues in a study of patients undergoing abdominal operations for Crohn's disease [5]. van Goor and colleagues isolated bacteria in mesenteric lymph nodes from 11 of 21 brain-dead organ donors with anatomically intact gastrointestinal tracts [150]. Sedman and colleagues found evidence of translocation to mesenteric lymph nodes in 10.3% of 267 patients undergoing general surgical procedures [132].

Braithwaite and colleagues used immunofluorescent staining of *Escherichia coli*-derived β-galactosidase (rather than standard microbiological methods) to document the presence of bacteria in macrophages in mesenteric lymph node specimens from every one of 20 trauma patients [13]. Unfortunately, in this study, samples from normal controls were not obtained and, therefore, it is unclear whether this represents a normal or a pathological occurrence. Reed and colleagues used both standard microbiological methods and electron microscopy to demonstrate bacteria in mesenteric lymph nodes from trauma victims [120]. As in the study by Braithwaite and colleagues already cited, samples from normal individuals were not studied. Certainly the most dramatic evidence that translocation can occur in humans comes in the form of a report by Krause, Matheis and Wulf, who documented that oral ingestion of a suspension of viable *C. albicans* resulted in transient fungaemia and funguria in a normal volunteer [70]. None of these studies, however, has demonstrated a correlation between the presence of viable (or non-viable) organisms in mesenteric nodes (or blood) and the development of multiple organ dysfunction syndrome (MODS).

Rush and colleagues showed a high incidence of bacteraemia and endotoxaemia in blood samples obtained from patients with haemorrhagic shock [127]. Since the samples were obtained within minutes after presentation to the emergency department, the development of bacteraemia in these patients presumably was not due to hospital-acquired infection. Interestingly, most of the isolates in this study were Gram-positive, rather than the enteric Gram-negative bacilli, which are most commonly isolated in studies of bacterial translocation using animal models of haemorrhagic shock. Thus, the implications of the findings obtained by Rush's group remain uncertain.

Winchurch, Thupari and Munster have shown that endotoxin is detectable in plasma samples obtained within 24 h after the time of injury from victims of thermal trauma [165]. Moreover, these workers have shown that the degree of endotoxaemia correlates with the magnitude of the injury. In a recent report from this group, however, it was shown that prophylactic treatment with an endotoxin-neutralizing antibiotic (polymyxin B) could lower the concentrations of circulating endotoxin detected in burns patients, but that this treatment effect was not associated with a lessening in mortality or with the concentrations of a cytokine (IL-6) in plasma [104]. Thus, Winchurch, Thupari and Munster concluded that the presence of endotoxaemia in burns patients may be an epiphenomenon rather than a primary factor leading to organ dysfunction.

Two other recent studies of trauma victims failed to validate the notion that bacterial translocation is increased in one important subpopulation of critically ill patients, namely those with multiple trauma. Moore and colleagues [102] were unable to detect elevated endotoxin concentrations in portal venous or systemic blood samples obtained over the first 5 days of hospitalization from 20 victims of major abdominal trauma, even though 60 % of the patients were in shock at the time of presentation and six of the subjects developed MODS. Although nine (2 %) of 424 systemic and portal venous blood cultures were positive over the 5-day period of observation, many of the isolates were probable contaminants. Cultures of ileocolic lymph nodes were positive in four of 12 cases, although in one case the isolated organism (*S. epidermidis*) was probably a contaminant.

Peitzman and coworkers [115] obtained biopsies of mesenteric lymph nodes at the time of coeliotomy from 25 trauma patients. Although 40 % of the trauma patients had one or more major complications, including adult respiratory distress syndrome (ARDS), serious pulmonary infections, and Gram-negative bacteraemia, all of the lymph node cultures were sterile. As a control for technique, the authors of this study also cultured lymph nodes obtained from patients with primary gastrointestinal tract diseases, and in three of four cases, were able to isolate enteric organisms. Thus, these two studies must be viewed as casting doubt on the idea that translocation of gut-derived bacteria or endotoxin plays a crucial role in the development of serious complications, at least in victims of major trauma.

During the past several years, a number of studies have documented the presence of gut mucosal hyperpermeability in human volunteers challenged with tiny doses of endotoxin [109], or patients with a variety of critical illnesses [27, 51, 110, 124, 125, 128, 170]. However, just as is the case for translocation, data are lacking to show that the presence of hyperpermeability is associated with or predicts the development of MODS.

Despite the "negative" studies just cited, the notion that the gut is somehow a pivotal organ in critical illness remains viable because of other circumstantial evidence from clinical studies. Certainly, it is well established that septic complications are diminished by providing early enteral nutrition to trauma patients [74, 101]. In addition, colonization of the proximal gastrointestinal tract with certain pathogens, particularly *Pseudomonas aeruginosa* and coagulase-negative *Staphylococcus*, is associated with subsequent development of intensive care unit-acquired infections caused by these same organisms [92, 93]. Thus, the role of the gut as a "motor of multiple organ failure" remains a controversial but tenable hypothesis.

Pathophysiological mechanisms responsible for gut barrier failure

The patholophysiological mechanisms responsible for gut barrier dysfunction in critically ill humans remain to be elucidated. Given the complex nature of the gut barrier, however, it seems probable that no single mechanism can explain all aspects of barrier dysfunction or all cases of barrier dysfunction precipitated by different causes.

MUCOSAL HYPOXIA

In general, the rate of oxygen consumption ($V\text{O}_2$) by tissues is determined by the metabolic demand and not by oxygen delivery ($D\text{O}_2$); this is a statement of Pflüger's law. Certain pathophysiological processes can, however, reduce $D\text{O}_2$ below a critical value ($D\text{O}_{2\text{crit}}$) such that $V\text{O}_2$ becomes supply-dependent [57]. Supply-dependency of $V\text{O}_2$ can occur as a result of tissue hypoperfusion, arterial hypoxaemia or anaemia. Hypermetabolism, secondary to sepsis and other critical illnesses, necessitates higher $V\text{O}_2$, and thereby a higher $D\text{O}_{2\text{crit}}$ [52]. Alone or in combination, these factors may limit intracellular $P\text{O}_2$ to levels inadequate to support normal mitochondrial respiration. There are two important effects of supply-dependent mitochondrial respiration. First, glycolytic metabolic rate is increased in an effort to preserve adequate intracellular concentrations of adenosine triphosphate (ATP) by substrate level phosphorylation of adenosine diphosphate (ADP). In contrast with oxidative phosphorylation, substrate level phosphorylation is associated with the production of protons; i.e. enhanced glycolytic rate leads to intracellular acidosis [100]. Second, if mitochondrial respiration is sufficiently limited, then intracellular concentrations of ATP are depleted. As will be discussed below, both intracellular acidosis and ATP depletion can lead to increases in intestinal epithelial permeability.

In the clinical setting, the most likely cause of intestinal mucosal hypoxia is mesenteric hypoperfusion. The architecture of the microcirculation of the intestinal villi may act to increase the susceptibility of the epithelium to hypoxic injury because of inadequate perfusion. Each villus is supplied by a single central arteriole, which is surrounded by an arbor of draining venules. Probably as a result of both counter current arteriovenous diffusional shunting of oxygen as well as consumption of oxygen by cells along the length of the villus, the tissue $P\text{O}_2$ at the tips of villi is low even under normal conditions. During low flow states, these conditions are exacerbated, further increasing the likelihood of supply-dependency of oxygen uptake [81, 82, 133].

Another factor which may predispose the villous epithelium to ischaemic injury during low-flow states is "plasma skimming" [67]. This phenomenon occurs because the nutrient arterioles supplying each villus originate at right angles to the parent artery. Since erythrocytes tend to cluster away from the walls of arteries, this architecture leads to relative haemodilution (and reduced oxygen carrying capacity) in the blood perfusing villous arterioles.

Two common conditions, which are likely to induce marked mesenteric ischaemia in critically ill patients, are haemorrhage and cardiogenic shock [17, 97, 98, 122]. Studies using animal models have documented that global decreases in cardiac output because of haemorrhage or cardiac tamponade lead to activation of the renin-angiotensin axis, which, in turn, triggers a dramatic increase in mesenteric arteriolar resistance [17, 97, 122]. Splanchnic hypoperfusion also has been reported in animal models after thermal injury [61, 103].

Sepsis is another common condition, which may be associated with mesenteric hypoperfusion. In contradistinction to haemorrhage or cardiogenic shock, however, the effects of sepsis on mesenteric (or mucosal) perfusion and oxygenation are poorly understood. Total hepatosplanchnic perfusion is elevated in humans with compensated sepsis [25, 48, 163]. Data are lacking regarding the effects of septic shock in humans on mesenteric and, particularly, intestinal mucosal perfusion.

We [36, 37, 130] and others [6, 119, 138, 161, 167] have documented that mesenteric perfusion is compromised in experimental models of sepsis and septic shock. Interestingly, however, we have never been able to document a decrease in transmesenteric $V\text{O}_2$ in endotoxaemic pigs [36, 37, 130]. Other investigators have reported similar findings [7, 119, 151]. In other words, transmesenteric oxygen extraction seems to be increased sufficiently in sepsis to maintain normal (or even elevated) levels of $V\text{O}_2$. Nevertheless, ileal mucosal acidosis is a characteristic feature of sepsis in experimental animals [36, 37, 119, 130]. Gastric mucosal acidosis occurs commonly in septic patients [49, 88, 135].

The development of gastrointestinal mucosal acidosis in sepsis, whether in animals models or patients, has been interpreted as evidence of gut epithelial hypoxia. However, normalization of superior mesenteric arterial blood flow ameliorates but does not completely normalize endotoxin-induced mucosal acidosis in pigs [36], a finding which suggests that mechanisms other than, or in addition to, mucosal ischaemia might contribute to tissue acidosis in sepsis. To further investigate this issue, we recently conducted an experimental study using a resuscitated, normodynamic pig model of endotoxaemic shock [152]. Mucosal oxygenation was measured directly using an array of eight Clark-type tissue $P\text{O}_2$ microelectrodes. Mucosal perfusion and acidosis were measured by laser Doppler flowmetry and intraluminal tonometry, respectively. After infusion of endotoxin, pigs developed ileal mucosal acidosis despite the absence of any significant change in mucosal blood flow and a significant *increase* in mucosal oxygen tension ($P\text{m}_{\text{O}_2}$). These observations are consistent with previous findings obtained by Hurtado and colleagues, who showed that lactic acidosis develops in skeletal muscle of septic rabbits despite normal tissue oxygenation [62]. Although an unexpected finding, the increase in $P\text{m}_{\text{O}_2}$ induced by endotoxin can be explained on the basis of the Bohr effect (i.e. an increased unloading of oxygen from haemoglobin as a result of acidosis) [75].

OXIDANT STRESS

Oxidants have been implicated in a variety of causes of intestinal barrier dysfunction. In experimental animals, intestinal ischaemia followed by reperfusion leads to mucosal hyperpermeability and biochemical evidence of oxidant stress [44, 45]. During the reperfusion phase, spin trapping techniques have been used to demonstrate the formation of free radicals [108]. There are two main sources of reactive oxygen metabolites (ROM) in intestinal ischaemia/reperfusion: (1) the reaction catalysed by xanthine oxidase and (2) the reaction catalysed by NADPH oxidase in neutrophils sequestered in the intestinal microvasculature. Agents which scavenge ROM or inhibit xanthine oxidase have been shown to ameliorate derangements in intestinal barrier function after intestinal ischaemia/reperfusion [112]. These strategies also have been shown to have salutary effects on barrier function in animals subjected to haemorrhage [28, 29] or systemic inflammation [30, 32, 85].

The mechanisms whereby oxidants impair barrier function are not well understood. In various *in vitro* models, however, oxidants, such as hydrogen peroxide (H_2O_2) or superoxide radical ($O_2^-\cdot$) have been shown to increase the permeability of epithelial [160] or endothelial [55] monolayers, and also disrupt the cytoskeleton (by promoting excessive actin polymerization) [55, 56]. Although most research related to alterations in epithelial (or endothelial) permeability and the actin-based cytoskeleton have focused on the paracellular pathway, it is plausible that cytoskeletal derangements also promote increased endo- and transcytosis. Sundqvist and Liu reported that endocytosis of FITC-dextran (70000 Da) is promoted when cultured endothelial monolayers are incubated with H_2O_2, an oxidant known to cause cytoskeletal destabilization [141]. Bhalla and Crocker reported that exposure of tracheal epithelial cells to ozone, another potent oxidant, promotes vesicular transcytosis of a macromolecule (horseradish peroxidase) [9]. Thus oxidant-induced epithelial damage might promote barrier dysfunction via transcellular as well as paracellular pathways.

ROM can lead to ATP depletion [53, 54, 164]. As will be discussed below, ATP depletion is another potential factor contributing to epithelial barrier dysfunction. The mechanisms responsible for oxidant-mediated ATP depletion probably include inhibition of glyceraldehyde-3-phosphate dehydrogenase (in the glycolytic pathway) and inhibition of mitochondrial phosphorylation of ADP [64].

MUCOSAL ACIDOSIS

In an effort to maintain adequate energy levels, hypoxic cells increase their rate of anaerobic metabolism (i.e. glycolysis). In contradistinction to oxidative phosphorylation, substrate level phosphorylation of ADP during glycolysis leads to a net release of protons. Under anaerobic conditions, there is net formation of two moles of H^+ per mole of glucose metabolized (at physiological pH) [100]. Since anaerobic metabolism is less efficient than oxidative metabolism for generating high-energy compounds, hypoxia results in ATP depletion. In sepsis, tissue acidosis can occur even in the absence of hypoperfusion or hypoxia [60, 152]. Sepsis downregulates the activity of pyruvate dehydrogenase (PDH), the enzyme complex catalysing the first irreversible step in the mitochondrial oxidative pathway [153]. The shift of PDH to its inactive form in sepsis fosters increased flux through the glycolytic pathway without a commensurate increase in mitochondrial oxidative phosphorylation. Glycolytic flux also may be increased in sepsis as a result of increased availability of glucose transporters on the surface of cells [169].

Since acidosis is an inevitable consequence of cellular hypoxia, tissue pH might be a useful variable to monitor in critically ill patients. Indeed, low gastric intramural pH has been shown to predict the development of MODS, mortality, or both in critically ill patients [23, 34, 39, 50, 96, 126, 168]. Interestingly, in a recent study of the effects of intestinal ischaemia induced by systemic endotoxaemic or partial mechanical occlusion of the mesenteric artery in pigs, we noted that there was a strong correlation between the degree of mucosal tissue acidosis and the degree of ileal mucosal hyperpermeability induced by these perturbations [130]. This finding suggested to us that the adverse effects of ischaemia on intestinal epithelial permeability might be related to the resultant derangements in tissue pH rather than simply the changes in tissue oxygenation *per se*. In an effort to further investigate this possibility, we employed a porcine preparation to examine the effects of mucosal acidosis induced by deliberately increasing arterial carbon dioxide tension, and observed a substantial increase in ileal epithelial permeability, even in the absence of findings indicative of mucosal ischaemia or dysoxia [130]. In other studies, using cultured Caco-2_{BBe} cells as a model of the intestinal epithelium, we have shown that acidosis similarly increases permeability *in vitro* [unpublished observations].

The mechanism(s) whereby acidosis promotes epithelial hyperpermeability are unknown. It has been established, however, that acidosis can promote the formation of oxidants. A number of studies have shown that acidosis promotes lipid peroxidation [14, 19, 105, 121, 134] or other manifestations [111] of oxidant-mediated damage in cells. Acidosis promotes mobilization of free iron from intracellular stores [15, 113], and evidence has been presented supporting the view that oxidant stress under conditions of acidosis depends, at least in part, on iron delocalization [113]. Recent findings [123] suggest that another mechanism whereby acidosis enhances oxidant-mediated damage is inhibition of two key enzymes: glutathione reductase, which is required to regenerate reduced glutathione (GSH); and glutathione peroxidase, which uses GSH to convert H_2O_2 to water.

Another way that acidosis might alter epithelial permeability is increasing intracellular calcium concentration ($[Ca^{2+}]_i$) [18]. Possible mechanisms for the tendency of low pH_i to increase $[Ca^{2+}]_i$ in epithelial cells include increased mitochondrial Ca^{2+}–H^+ exchange, modulation of Ca^{2+} flux into the smooth ER, and activation of a pH-dependent plasma membrane Ca^{2+} channel [18]. Elevations in *intracellular* $[Ca^{2+}]$ loosen tight junctions and increase intestinal epithelial permeability. In hepatocytes, paracellular permeability is increased by a number of agents which increase $[Ca^{2+}]_i$, including: certain hormones (e.g. vasopressin) [80], a calcium ionophore (A23187) [66], and a calcium-mobilizing agent (tBuGHQ) [38]. In cultured MDCK (renal epithelial) monolayers, exposure to A23187 increases permeability [116]. The effects of increased $[Ca^{2+}]_i$ on intestinal epithelial permeability have not been investigated.

ATP DEPLETION

As noted above, ATP depletion is a consequence of impaired mitochondrial function, the result of intracellular hypoxia. ATP depletion can also be caused by oxidant stress, leading to inhibition of glyceraldehyde-3-phosphate dehydrogenase (in the glycolytic pathway) and inhibition of mitochondrial phosphorylation of ADP [64]. Acidosis, in a form of positive feedback, can also promote ATP depletion

[140], perhaps by inhibiting the rate-limiting phosphofructokinase step in glycolysis [20, 145] or via other poorly understood mechanisms [140].

In order to investigate the role of ATP depletion as a factor leading to intestinal hyperpermeability we recently studied the effects of chronic hypoxia or glycolytic inhibition with 2-deoxyglucose (2-DOG) on Caco-2_{BBe} monolayers [146]. In both scenarios, we found that relatively minor reductions ($< 30\%$) in ATP content were sufficient to increase the permeability of Caco-2_{BBe} monolayers. The mechanism appears to involve derangements in the actin-based cytoskeleton, since laser confocal micrographs using rhodamine-phalloidin to stain polymerized (F) actin demonstrated perijunctional condensation of actin filaments after prolonged 2-DOG exposure.

Although it is well established that ATP depletion increases epithelial [71, 76, 87, 146] and endothelial permeability [157], the precise mechanism(s) underlying this phenomenon are not established. It is known that ATP depletion disrupts actin microfilaments [56, 71] by fostering the conversion of monomeric (G) actin to F-actin [56, 99]. As noted above, proper functioning of the actin-based cytoskeleton is essential for the maintenance of normal epithelial permeability characteristics. The tendency for actin to polymerise under conditions of ATP depletion (27, 28, 34) is paradoxical, since *in vitro*, the polymerization of G-actin to F-actin is an energy-requiring event, which depends upon the irreversible hydrolysis of ATP (35). Only tiny quantities of G-actin are required for filament growth *in vitro*, thus, at equilibrium, the majority of actin *in vitro* is present in its polymerized form (36). *In vivo*, however, approximately half of the actin in cells is present in its monomeric form (36). No adequate explanation has been advanced to explain this paradox, but we hypothesize that ATP depletion may foster cytoskeletal derangements by interfering with normal intracellular calcium homeostasis.

NITRIC OXIDE

Produced by mammalian cells from the amino acid, L-arginine, the small molecule, nitric oxide (NO·), has been identified as an important regulator and/or effector of many phenomena in the cardiovascular, nervous, and immune systems [106]. Increasingly, it is apparent that NO· also plays a versatile role in the physiology and pathophysiology of the gastrointestinal tract [137].

The reaction responsible for the formation of NO· is catalysed by a family of enzymes called nitric oxide synthase (NOS) [68, 90]. There are three isoforms of this enzyme, including: neuronal or type I NOS found primarily in neuronal tissues and skeletal muscle; endothelial or type III NOS (eNOS), found primarily in endothelial cells; and inducible or type II NOS found in a wide variety of cell types, including macrophages and hepatocytes. Both nNOS and eNOS are constitutively expressed, and the production of NO· by these enzymes is dependent on the presence of calmodulin and intracellular concentrations of Ca^{2+}. In contrast, iNOS contains calmodulin as a tightly bound subunit even under nominally Ca^{2+}-free conditions, and the enzyme is expressed only after induction by various cytokines or LPS.

A large variety of cell types in the gut are potential sources of NO·. These cell types include myenteric neurons [16, 78, 107, 156], vascular endothelial cells [107, 117] and interstitial cells of Cajal [118]. Inflammatory cells in the submucosa, including mast cells [58], macrophages [43, 139], and polymorphonuclear leucocytes [47, 85], are capable of producing NO·. Luminal bacteria represent another potential source of NO· in the gastrointestinal tract [41].

Enterocytes also appear to be capable of producing NO·, at least under certain conditions. Boughton-Smith and colleagues reported that iNOS activity is elevated in biopsy specimens of inflamed colonic mucosa from patients with ulcerative colitis [10]. These investigators have also documented that administration of LPS to rats leads to the induction of iNOS activity in homogenates of jejunal or colonic tissue [11]. These results suggest that various inflammatory states (e.g. ulcerative colitis and acute endotoxicosis) are associated with induction of iNOS activity in gut epithelial cells, although the observed data also could be explained by iNOS induction in resident or infiltrating inflammatory cells in the mucosa or lamina propria. Tepperman and colleagues, however, have documented upregulation of iNOS activity in isolated enterocytes harvested from the colons of rats injected 4 h earlier with LPS [142]. Furthermore, these workers have shown that prior administration of an anti-neutrophil antiserum prevents LPS-induced leucosequestration in the colonic mucosa, but has no effect on measured concentrations of iNOS activity, supporting the view that infiltrating neutrophils are not the source of the iNOS activity in enterocytic preparations from endotoxic rats.

The idea that enterocytes can be induced to produce NO· is further supported by preliminary findings obtained by several laboratories. For example, Grisham has demonstrated that exposure of cultured IEC-18 (rat intestinal epithelial) cells to LPS, IL-1, or TNF-α plus IFN-γ, increases production of nitrite plus nitrate (markers of NO· production) [46]. Dignass, Podolsky and Rachmilewitz showed that incubation of cultures of another rat enterocytic cell line (IEC-6) with a number of different cytokines (e.g. IL-2, TNF-α) results in modest increases in the production of nitrogen oxides [33]. Recently, our group has shown that incubation of Caco-2_{BBe} cells with the pro-inflammatory cytokine, IFN-γ, increases the release of markers of increased NO· production (nitrite and nitrate anions) into the media [147]. Even more recently, we have shown that incubation of Caco-2_{BBe} cells with INF-γ upregulates expression of iNOS mRNA [unpublished observations].

NO· appears to be capable of modulating intestinal epithelial permeability. Interestingly, depending upon the experimental system employed, NO· can either diminish or increase intestinal permeability to various water-soluble molecules. The idea that NO· plays a beneficial role to preserve normal gut barrier function is supported by a number of observations. In 1992, Kubes reported that infusion of a NOS inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), into the mesenteric artery of cats markedly increases ileal epithelial permeability to a hydrophilic probe [72]. In a subsequent study, Payne and Kubes documented that infusion of an NO· donor, such as sodium nitroprusside (SNP) or exogenous arginine (NOS substrate) ameliorates gut mucosal hyperpermeability induced by ischaemia/reperfusion [114]. Using a similar design, Boughton-Smith and colleagues showed that infusion of an NO· donor compound can ameliorate gut mucosal damage induced by intravenous injection of LPS in rats [12]. Conversely, treatment with NOS inhibitors has been shown to exacerbate gut epithelial hyperpermeability induced by ischaemia/reperfusion [73] and macroscopic mucosal damage induced by LPS [63]. Therefore, data from a number of *in vivo* studies support the following conclusions: (1) under basal conditions, endogenous production of NO· serves to maintain normal permeability of the intestinal mucosa; (2) under basal conditions, blocking NO· synthesis increases gut mucosal permeability; (3) in certain pathological conditions associated with derangements in gut mucosal barrier function and/or integrity (e.g. ischaemia/reperfusion injury or endotoxicosis), provision of exogenous NO· tends to maintain normal intestinal epithelial structure and function; (4) in these same pathological conditions, blockade of NO· biosynthesis tends to exacerbate derangements in the structural and functional integrity of the mucosa.

In contrast with these findings are other data which suggest that overproduction of NO· can be deleterious to the integrity of the intestinal mucosal barrier. For example, Lopez-Belmonte, Whittle and Moncada showed that close arterial infusion of NO donors, SNP or *S*-nitroso-*N*-acetylpenicillamine (SNAP), causes gastric mucosal damage in the rat when infused at high concentrations [79]. Similarly, Tepperman and colleagues reported that NO· donors, such as SNP or SNAP, decrease the *ex vivo* viability of freshly harvested rat colonic epithelial cells [142]. Tepperman and colleagues also showed that *in vivo* administration of LPS decreases the viability of gut epithelial cells via an NO·-dependent mechanism [142, 143]. Recently, our group demonstrated that NO· donors (SNP or SNAP) as well as authentic NO· gas are capable of increasing the permeability of Caco-2_{BBe} monolayers to a variety of hydrophilic macromolecules [129]. The deleterious effect of NO· on barrier function appears to be mediated through derangements in intracellular ATP production and cytoskeletal organization [129].

CYTOKINES

Recent studies performed using cultured T_{84} enterocytic cells suggest that certain proinflammatory cytokines, namely IFN-γ and IL-4, are capable of increasing the permeability of model epithelia [1, 24, 84]. The mechanism(s) whereby cytokines, such as IFN-γ, induce intestinal epithelial hyperpermeability have not been determined. It is known, however, that IFN-γ, acting either alone or in combination with other cytokines, is capable of triggering increased production of NO· by a number of different cell types [69, 89, 154, 162]. Thus, it seems plausible that cytokine-induced intestinal epithelial hyperpermeability is mediated through induction iNOS leading excess NO· production. In support of this view are recent data published by our group, showing that: (1) incubation of Caco-2_{BBe} (enterocytic) cells with IFN-γ increases the release of NO· oxidation products (nitrite and nitrate) into culture supernatants; (2) Caco-2_{BBe} monolayers can be rendered hyperpermeable by incubation in media containing IFN-γ; and (3) coincubation of Caco-2_{BBe} monolayers with INF-γ and various NOS inhibitors significantly blunts the development of hyperpermeability [147].

Conclusions

Although attractive on theoretical grounds, the notion that gut barrier dysfunction contributes to morbidity, including MODS, in critically ill patients remains unproved. Despite the presence of negative data, however, this concept remains a fruitful line of investigation both at the bedside and in the laboratory. At the very least, learning about the mechanisms underlying gut barrier failure in critical illness will provide insights into the mechanisms of cellular dysfunction of all kinds associated with sepsis or other causes of diffuse inflammation. At best, this avenue of investigation will lead to improvements in management and a reduction in morbidity and mortality in victims of trauma, sepsis or other acute life-threatening illnesses.

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References

1. Adams RB, Planchon SM, Roche JK. IFN-γ modulation of epithelial barrier function: time course, reversibility, and site of cytokine binding. *Journal of Immunology* 1993; **150**: 2356–2363.
2. Alexander JW, Boyce ST, Babcock GF, Gianotti L, Peck MD, Dunn DL, Pyles T, Childress CP, Ash SK. The process of microbial translocation. *Annals of Surgery* 1990; **212**: 496–510.
3. Alverdy J. The effect of glucocorticoid administration on bacterial translocation: evidence for an acquired mucosal immunodeficient state. *Annals of Surgery* 1991; **214**: 719–723.
4. Alverdy JC, Aoys E. The effect of dexamethasone and endotoxin administration on biliary IgA and bacterial adherence. *Journal of Surgical Research* 1992; **53**: 450–454.
5. Ambrose NS, Johnson M, Burdon DW, Keighley MRB. Incidence of pathogenic bacteria from mesentric lymph nodes and ilea serosa during Crohn's disease surgery. *British Journal of Surgery* 1984; **71**: 623–625.
6. Antonsson JB, Kuttila K, Niinikoski J, Haglund UH. Subcutaneous and gut tissue perfusion and oxygenation changes as related to oxygen transport in experimental peritonitis. *Circulatory Shock* 1993; **41**: 261–267.
7. Arvidsson D, Rasmussen I, Almqvist P, Niklasson F, Haglund U, Splanchnic oxygen consumption in septic and hemorrhagic shock. *Surgery* 1991; **109**: 190–197.
8. Beagley KW, Elson CO. Cells and cytokines in mucosal immunity and inflammation. *Gastroenterology Clinics of North America* 1992; **21**: 347–366.

9. Bhalla DK, Crocker TT. Tracheal permeability in rats exposed to ozone. *American Review of Respiratory Disease* 1986; **134**: 572–579.
10. Boughton-Smith NK, Evans SM, Hawkey CJ, Cole AT, Balsitis M, Whittle BJ, Moncada S. Nitric oxide synthase activity in ulcerative colitis and Crohn's disease. *Lancet* 1993; **342**: 338–340.
11. Boughton-Smith NK, Evans SM, Laszlo F, Whittle BJ, Moncada S. The induction of nitric oxide synthase and intestinal vascular permeability by endotoxin in the rat. *British Journal of Pharmacology* 1993; **110**: 1189–1195.
12. Boughton-Smith NK, Hutcheson IR, Deakin AM, Whittle BJR, Moncada S. Protective effect of S-nitroso-N-acetyl-penicillamine in endotoxin-induced acute intestinal damage in the rat. *European Journal of Pharmacology* 1990; **191**: 485–488.
13. Braithwaite CEM, Ross SE, Nagele R, Mure AJ, O'Malley KF, Garcia-Perez FA. Bacterial translocation occurs in humans after traumatic injury: evidence using immunofluorescence. *Journal of Trauma* 1993; **34**: 586–590.
14. Bralet J, Bouvier C, Schrieber L, Boquillon M. Effect of acidosis on lipid peroxidation in brain slices. *Brain Research* 1991; **539**: 175–177.
15. Bralet J, Schreiber L, Bouvier C. Effect of acidosis and anoxia on iron delocalization from brain homogenates. *Biochemical Pharmacology* 1992; **43**: 979–983.
16. Bredt DS, Snyder SH. Localization of nitric oxide synthase indicating a neural role for nitric oxide. *Nature* 1990; **347**: 768–770.
17. Bulkley GB, Kvietys PR, Parks DA, Perry MA, Granger DN. Relationship of blood flow and oxygen consumption to ischemic injury in the canine small intestine. *Gastroenterology* 1985; **89**: 852–857.
18. Burns KD, Homma T, Breyer MD, Harris RC. Cytosolic acidification stimulates a calcium influx that activates Na^+–H^+ exchange in LLC-PKX1 cells. *American Journal of Physiology* 1991; **261**: F617–F625.
19. Cancela JM, Bralet J, Beley A. Effects of iron-induced lipid peroxidation and of acidosis on choline uptake by synaptosomes. *Neurochemical Research* 1994; **19**: 833–837.
20. Carpenter JF, Hand SC. Reversible dissociation and inactivation of phosphofructokinase in ischemic rat heart. *American Journal of Physiology* 1986; **250**: R512–R518.
21. Cerf-Bensussan N, Guy-Grand D. Intestinal epithelial lymphocytes. *Gastroenterology Clinics of North America* 1991; **20**: 549–576.
22. Chadwick VS, Mellor DM, Meyers DB, Selden AC, Keshavarzian A, Broom MF, Hobson CH. Production of peptides inducing chemotaxis and lysozomal enzyme release in human neutrophils by intestinal bacteria in vitro and in vivo. *Scandinavian Journal of Gastroenterology* 1988; **23**: 121–128.
23. Chang MC, Cheatham ML, Nelson LD, Rutherford EJ, Morris JA, jr. Gastric tonometry supplements information provided by systemic indicators of oxygen transport. *Journal of Trauma* 1994; **37**: 488–494.
24. Colgan SP, Resnick MB, Parkos CA, Delp-Archer C, McGuirk D, Bacarra AE, Weller PF, Madara JL. IL-4 directly modulates function of a model human intestinal epithelium. *Journal of Immunology* 1994; **153**: 2122–2129.
25. Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA. Splanchnic and total body oxygen consumption differences in septic and injured patients. *Surgery* 1987; **101**: 69–80.
26. Deitch EA. Simple intestinal obstruction causes bacterial translocation in man. *Archives of Surgery* 1989; **124**: 699–701.
27. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. *Surgery* 1990; **107**: 411–416.
28. Deitch EA, Bridges W, Baker J, Ma J-W, Ma L, Grisham MB, Granger DN, Specian RD, Berg R. Hemorrhagic shock-induced bacterial translocation is reduced by xanthine oxidase inhibition or inactivation. *Surgery* 1988; **104**: 191–198.
29. Deitch EA, Bridges W, Baker J, Ma JW, Ma L, Grisham MB, Granger DN, Specian RD, Berg R. Hemorrhagic shock-induced bacterial translocation is reduced by xanthine oxidase inhibition or inactivation. *Surgery* 1988; **104**: 191–198.
30. Deitch EA, Ma L, Ma JW, Grisham MB, Granger DN, Specian RD, Berg RD. Inhibition of endotoxin-induced bacterial translocation in mice. *Journal of Clinical Investigation* 1989; **84**: 36–42.
31. Deitch EA, Morrison J, Berg R, Specian RD. Effect of hemorrhagic shock on bacterial translocation, intestinal morphology, and intestinal permeability in conventional and antibiotic-decontaminated rats. *Critical Care Medicine* 1990; **18**: 529–536.
32. Deitch EA, Specian RD, Berg RD. Endotoxin-induced bacterial translocation and mucosal permeability: role of xanthine oxidase, complement activation, and macrophage products. *Critical Care Medicine* 1991; **19**: 785–791.
33. Dignass A, Podolsky D, Rachmilewitz D. Nitric oxide generation by intestinal epithelial cells is stimulated by cytokines and bacterial endotoxin. *Gastroenterology* 1994; **106**: A673.
34. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19**: 1037–1040.
35. Fink MP, Antonsson JB, Wang H, Rothschild HR. Increased intestinal permeability in endotoxic pigs: mesenteric hypoperfusion as an etiologic factor. *Archives of Surgery* 1991; **126**: 211–218.
36. Fink MP, Kaups KL, Wang H, Rothschild HR. Maintenance of superior mesenteric arterial perfusion prevents increased intestinal mucosal permeability in endotoxic pigs. *Surgery* 1991; **110**: 154–161.
37. Fink MP, Rothschild HR, Deniz YF, Wang H, Lee PC, Cohn SM. Systemic and mesenteric O_2 metabolism in endotoxic pigs: effect of ibuprofen and meclofenamate. *Journal of Applied Physiology* 1989; **67**: 1950–1957.
38. Fleming I, Gray GA, Stoclet J-C. Influence of endothelium on induction of the L-arginine-nitric oxide pathway in rat aortas. *American Journal of Physiology* 1993; **264**: H1200–H1207.
39. Frenette L, Doblar DD, Singer D, Cox J, Ronderos J, Poplawski S, Ranjan D. Gastric intramural pH as indicator of early graft viability in orthotopic liver transplantation. *Transplantation* 1994; **58**: 292–297.
40. Fukushima R, Gianotti L, Alexander JW, Pyles T. The degree of bacterial translocation is a determinant factor for mortality after burn injury and is improved by prostaglandin analogs. *Annals of Surgery* 1992; **216**: 438–445.
41. Goretski J, Zafiriou OC, Hollocher TC. Steady-state nitric oxide concentrations during denitrification. *Journal of Biological Chemistry* 1990; **265**: 11535–11538.
42. Goris RJ, Beokhorst PA, Nuytinck KS. Multiple organ failure: generalized autodestructive inflammation. *Archives of Surgery* 1986; **120**: 1109–1115.
43. Granger DL, Hibbs JB, Perfect JR, Durack DT. Metabolic fat of L-arginine in relation to microbiostatic capability of murine macrophages. *Journal of Clinical Investigation* 1990; **85**: 264–273.
44. Granger DN. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. *American Journal of Physiology* 1988; **255**: H1269–H1275.
45. Granger DN, Rutili G, McCord JM. Superoxide radicals in feline intestinal ischemia. *Gastroenterology* 1981; **81**: 22–29.
46. Grisham MB. Nitric oxide production by intestinal epithelial cells. *Gastroenterology* 1993; **104**: A710.
47. Grisham MB, Ware K, Gilleland HE, Jr, Gilleland LB, Abell CL, Yamada T. Neutrophil-mediated nitrosamine formation: role of nitric oxide in rats. *Gastroenterology* 1992; **103**: 1260–1266.
48. Gump FE, Price JG, Kinney JM. Whole body and splanchnic blood flow in oxygen consumption measurements in patients with intraperitoneal infection. *Annals of Surgery* 1970; **171**: 321–328.
49. Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C. Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 324–329.
50. Gys T, Hubens A, Neels H, Lauwers LF, Peeters R. Prognostic value of gastric intramural pH in surgical intensive care patients. *Critical Care Medicine* 1988; **16**: 1222–1224.

51. Harris CE, Griffiths RD, Freestone N, Billington D, Atherton ST, Macmillan RR. Intestinal permeability in the critically ill. *Intensive Care Medicine* 1992; **18**: 38–41.
52. Heard SO, Baum TD, Wang H, Rothschild HR, Fink MP. Systemic and mesenteric O_2 metabolism in endotoxic pigs: effect of graded hemorrhage. *Circulatory Shock* 1991; **35**: 44–52.
53. Hinshaw DB, Burger JM, Protective effect of glutamine on endothelial cell ATP in oxidant injury. *Journal of Surgical Research* 1990; **49**: 222–227.
54. Hinshaw DB, Burger JM, Armstrong BC, Hyslop PA. Mechanism of endothelial cell shape change in oxidant injury. *Journal of Surgical Research* 1989; **46**: 339–349.
55. Hinshaw DB, Burger JM, Beals TF, Armstrong BC, Hyslop PA. Actin polymerization in cellular oxidant injury. *Archives of Biochemistry and Biophysics* 1991; **288**: 311–316.
56. Hinshaw DB, Burger JM, Miller MT, Adams JA, Beals TF, Omann GM. ATP depletion induces an increase in the assembly of a labile pool of polymerized actin in endothelial cells. *American Journal of Physiology* 1993; **264**: C1171–C1179.
57. Hochachka PW. Metabolic suppression and oxygen availability. *Canadian Journal of Zoology* 1987; **66**: 152–158.
58. Hogaboam CM, Befus AD, Wallace JL. Modulation of rat mast cell reactivity by IL-1β: divergent effects on nitric oxide and platelet activating factor release. *Journal of Immunology* 1993; **151**: 1267–3774.
59. Horton JW. Alterations in intestinal permeability and blood flow in a new model of mesenteric ischemia. *Circulatory Shock* 1992; **36**: 134–139.
60. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *Journal of the American Medical Association* 1992; **267**: 1503–1509.
61. Huang KF, Chung DH, Herndon DN. Insulinlike growth factor 1 (IGF-1) reduces gut atrophy and bacterial translocation after severe burn injury. *Archives of Surgery* 1993; **128**: 47–54.
62. Hurtado FJ, Gutierrez AM, Silva N, Fernandez E, Khan AE, Gutierrez G. Role of tissue hypoxia as the mechanism of lactic acidosis during *E. coli* endotoxemia. *Journal of Applied Physiology* 1992; **72**: 1895–1901.
63. Hutcheson IR, Whittle BJ, Boughton-Smith NK. Role of nitric oxide in maintaining vascular integrity in endotoxin-induced intestinal damage in the rat. *British Journal of Pharmacology* 1990; **101**: 815–820.
64. Hyslop PA, Hinshaw DB, Halsey WA jr, Schraufstatter IU, Sauerheber RD, Spragg RG, Jackson JH, Cochrane CG. Mechanism of oxidant-mediated cell injury: the glycolytic and mitochondrial pathways of ADP phosphorylation are major intracellular targets inactivated by hydrogen peroxide. *Journal of Biological Chemistry* 1988; **253**: 1665–1675.
65. James SP. The gastrointestinal mucosal immune system. *Digestive Diseases* 1993; **11**: 146–156.
66. Kan KS, Coleman R. The calcium ionophore A23187 increases the tight-junctional permeability in rat liver. *Biochemical Journal* 1988; **256**: 1039–1041.
67. Kiel JW, Riedel GL, Shepherd AP. Effects of hemodilution on gastric and intestinal oxygenation. *American Journal of Physiology* 1989; **256**: H171–H178.
68. Knowles RG, Moncada S. Nitric oxide synthases in mammals. *Biochemical Journal* 1994; **298**: 249–258.
69. Koide M, Kawahara Y, Tsuda T, Nakayama I, Yokoyama M. Expression of nitric oxide synthase by cytokines in vascular smooth muscle cells. *Hypertension* 1994; **23**: 145–148.
70. Krause W, Matheis H, Wulf K. Fungaemia and funguria after oral administration of *Candida albicans*. *Lancet* 1969; **1**: 598–600.
71. Kroshian VM, Sheridan AM. Lieberthal W. Functional and cytoskeletal changes induced by sublethal injury in proximal tubular epithelial cells. *American Journal of Physiology* 1994; **266**: F21–F30.
72. Kubes P. Nitric oxide modulates epithelial permeability in the feline small intestine. *American Journal of Physiology* 1992; **262**: G1138–G1142.
73. Kubes P. Ischemia-reperfusion in the feline small intestine: a role for nitric oxide. *American Journal of Physiology* 1993; **264**: G143–G149.
74. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO. Enteral *versus* parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. *Annals of Surgery* 1992; **215**: 503–513.
75. Kwant G, Oeseburg B, Zwart A, Zijlstra WG. Human whole-blood O_2 affinity: effect of CO_2. *Journal of Applied Physiology* 1988; **64**: 2400–2409.
76. Li C, Poznanasky MJ. Effect of FCCP on tight junction permeability and cellular distribution of ZO-1 protein in epithelial (MDCK) cells. *Biochemica et Biophysica Acta* 1990; **1030**: 297–300.
77. Lichtman SN, Okoruwa EE, Keku J, Schwab JH, Sartor RB. Degradation of endogenous bacterial cell wall polymers by the muralytic enzyme mutanolysin prevents hepatobiliary injury in genetically susceptible rats with experimental intestinal bacterial overgrowth. *Journal of Clinical Investigation* 1992; **90**: 1313–1322.
78. Llewellyn-Smith IJ, Song Z-M, Costa M, Bredt DS, Snyder SH. Ultrastructural localization of nitric oxide synthase immunoreactivity in guinea-pig enteric neurons. *Brain Research* 1992; **577**: 337–342.
79. Lopez-Belmonte J, Whittle BJ, Moncada S. The actions of nitric oxide donors in the prevention or induction of injury to the rat gastric mucosa. *British Journal of Pharmacology* 1993; **108**: 73–78.
80. Lowe PJ, Miyai K, Steinbach JH, Hardison WGM. Hormonal regulation of hepatocyte tight junctional permeability. *American Journal of Physiology* 1988; **255**: G454–G461.
81. Lundgren O. Studies on blood flow distribution and countercurrent exchange in the small intestine. *Acta Physiologica Scandinavia* (Supplement) 1967; **303**: 1–42.
82. Lundgren O. Microcirculation of the gastrointestinal tract and pancreas. In: *Handbook of Physiology. The Cardiovascular System. Microcirculation.* Bethesda, MD: American Physiological Society, 1984: 799–863.
83. Madara JL. Loosening tight junctions: lessons from the intestine. *Journal of Clinical Investigation* 1989; **83**: 1089–1094.
84. Madara JL, Stafford J. Interferon-γ directly affects barrier function of cultured intestinal epithelial monolayers. *Journal of Clinical Investigation* 1989; **83**: 724–727.
85. Mainous MR, Xu D, Deitch EA. Role of xanthine oxidase and prostaglandins in inflammatory-induced bacterial translocation. *Circulatory Shock* 1993; **40**: 99–104.
86. Malzwista SE, Montgomery RR, van Blaricom G. Evidence for reactive nitrogen intermediates in killing of staphylococci by human neutrophil cytoplasts. A new microbicidal pathway for polymorphonuclear leukocytes. *Journal of Clinical Investigation* 1992; **90**: 631–635.
87. Mandel LJ, Bacallao R, Zampighi G. Uncoupling of the molecular 'fence' and paracellular 'gate' functions in epithelial tight junctions. *Nature* 1993; **361**: 552–555.
88. Marik PE. Gastric intramucosal pH: a better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993; **104**: 225–229.
89. Markewitz BA, Michael JR, Kohan DE. Cytokine-induced expression of a nitric oxide synthase in rat renal tubule cells. *Journal of Clinical Investigation* 1993; **91**: 2138–2143.
90. Marletta MA. Nitric oxide synthase structure and mechanism. *Journal of Biological Chemistry* 1993; **268**: 12231–12234.
91. Marshall J, Sweeney D. Microbial infection and the septic response in critical surgical illness. *Archives of Surgery* 1990; **125**: 17–23.
92. Marshall JC, Christou NV, Horn R, Meakins JL. The microbiology of multiple organ failure: the proximal gastrointestinal tract as an occult reservoir of pathogens. *Archives of Surgery* 1988; **123**: 309–315.
93. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract. The "undrained abscess" of multiple organ failure. *Annals of Surgery* 1993; **218**: 111–119.
94. Matthews JB, Awtrey CS, Thompson R, Hung T, Tally KJ, Madara JL. Na^+–K^+–$2Cl^-$ cotransport and Cl^- secretion evoked by heat-stable enterotoxin is microfilament dependent in T84 cells. *American Journal of Physiology* 1993; **265**: G370–G378,
95. Matthews JB, Tally KJ, Smith JA, Zeind AJ, Hrnjez BJ.

Activation of Cl secretion during chemical hypoxia by endogenous release of adenosine in intestinal epithelial monolayers. *Journal of Clinical Investigation* 1995; **96**: 117–125.

96. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *Journal of the American Medical Association* 1993; **270**: 1203–1210.
97. McNeill JR, Stark RD, Greenway CV. Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. *American Journal of Physiology* 1970; **219**: 1342–1347.
98. McNeill JR, Wilcox WC, Pang CCY. Vasopressin and angiotensin: reciprocal mechanisms controlling mesenteric conductance. *American Journal of Physiology* 1977; **232**: H260–H266.
99. Molitoris BA, Geerdes A, McIntosh JR. Dissociation of redistribution of Na^+,K^+-ATPase from its surface membrane actin cytoskeletal complex during cellular ATP depletion. *Journal of Clinical Investigation* 1991; **88**: 462–469.
100. Mommsen TP, Hochachka PW. Protons and anaerobiasis. *Science* 1983; **219**: 1391–1397.
101. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma-reduced septic morbidity. *Journal of Trauma* 1989; **29**: 916–923.
102. Moore FA, Moore EE, Poggetti R, McAnana OJ, Peterson VM, Abernathy CM, Parsons PE. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. *Journal of Trauma* 1991; **31**: 629–638.
103. Morris SE, Navaratnam N, Herndon DN. A comparison of effects of thermal injury and smoke inhalation on bacterial translocation. *Journal of Trauma* 1990; **30**: 639–643.
104. Munster AM, Smith-Meek M, Dickerson C, Winchurch RA. Translocation. Incidental phenomenon or true pathology? *Annals of Surgery* 1993; **218**: 321–327.
105. Musleh W, Bruce A, Malfroy B, Baudry M. Effects of EUK-8, a synthetic catalytic superoxide scavenger, on hypoxia- and acidosis-induced damage in hippocampal slices. *Neuropharmcology* 1994; **33**: 929–934.
106. Nathan C. Nitric oxide as a secretory product of mammalian cells. *FASEB Journal* 1992; **6**: 3051–3064.
107. Nichols K, Staines W, Krantis A. Nitric oxide synthase distribution in the rat intestine: a histochemical analysis. *Gastroenterology* 1993; **105**: 1651–1661.
108. Nilsson UA, Lundgren O, Haglind E, Bylund-Fellenius A-C. Radical production during in vivo intestinal ischemia and reperfusion in the cat. *American Journal of Physiology* 1989; **257**: G409–G414.
109. O'Dwyer ST, Michie HR, Ziegler TR, Revhaug A, Smith RJ, Wilmore DW. A single dose of endotoxin increases intestinal permeability in healthy humans. *Archives of Surgery* 1988; **123**: 1459–1464.
110. Ohri SK, Bjarnson I, Pathi V, Somasundaram S, Bowles CT, Keogh BE, Khagani A, Menzies I, Yacoub MH, Taylor KM. Cardiopulmonary bypass impairs small intestinal transport and increases gut permeability. *Annals of Thoracic Surgery* 1993; **55**: 1080–1086.
111. Okabe E, Kato Y, Kohno H, Hess ML, Ito H. Inhibition by free radical scavengers and by cyclooxygenase inhibitors of the effect of acidosis on calcium transport by masseter muscle sarcoplasmic reticulum. *Biochemical Pharmacology* 1985; **34**: 961–968.
112. Otamiri T. Oxygen radicals, lipid peroxidation, and neutrophil infiltration after small-intestinal ischemia and reperfusion. *Surgery* 1989; **105**: 593–597.
113. Oubidar M, Boquillon M, Marie C, Schreiber L, Bralet J. Ischemia-induced brain iron delocalization: effect of iron chelators. *Free Radical Biology and Medicine* 1994; **16**: 861–867.
114. Payne D, Kubes P. Nitric oxide donors reduce the rise in reperfusion-induced intestinal mucosal permeability. *American Journal of Physiology* 1993; **265**: G189–G195.
115. Peitzman AB, Udekwu AO, Ochoa J, Smith S. Bacterial translocation in trauma patients. *Journal of Trauma* 1991; **31**: 1083–1087.
116. Peterson MW, Gruenhaupt D. A23187 increases permeability of MDCK monolayers independent of phospholipase activation. *American Journal of Physiology* 1990; **259**: C69–C76.
117. Pique JM, Whittle BJR, Esplugues JV. The vasodilator role of endogenous nitric oxide in the rat gastric microcirculation. *European journal of Pharmacology* 1989; **174**: 293–296.
118. Publicover NG, Hammond EM, Sander KM. Amplification of nitric oxide signaling by interstitial cells isolated from canine colon. *Proceedings of the National Academy of Sciences of the United States of America* 1993; **90**: 2087–2091.
119. Rasmussen I, Haglund U. Early gut ischemia in experimental fecal peritonitis. *Circulatory Shock* 1992; **38**: 22–28.
120. Reed LL, Martin M, Manglano R, Newson B, Kocka F, Barrett J. Bacterial translocation following abdominal trauma in humans. *Circulatory Shock* 1994; **42**: 1–6.
121. Rehncrona S, Hauge HN, Siesjo BK. Enhancement of iron-catalyzed free radical formation by acidosis in brain homogenates: differences in effect by lactic acid and CO_2. *Journal of Cerebral Blood Flow and Metabolism* 1989; **9**: 65–70.
122. Reilly PM, MacGowan S, Miyachi M, Schiller HJ, Vickers S, Bulkley GB. Mesenteric vasoconstriction in cardiogenic shock in pigs. *Gastroenterology* 1992; **102**: 1968–1979.
123. Rodeheaver DP, Schnellman RG. Extracellular acidosis ameliorates metabolic-inhibitor-induced and potentiates oxidant-induced cell death in renal proximal tubules. *Journal of Pharmacology and Experimental Therapeutics* 1993; **265**: 1355–1360.
124. Roumen RMH, Hendriks T, Wevers RA, Goris JA. Intestinal permeability after severe trauma and hemorrhagic shock is increased without relation to septic complications. *Archives of Surgery* 1993; **128**: 453–457.
125. Roumen RMH, van der Vliet JA, Wevers RA, Goris RJA. Intestinal permeability is increased after major vascular surgery. *Journal of Vascular Surgery* 1993; **17**: 734–737.
126. Roumen RMH, Vreugde JPC, Goris RJA. Gastric tonometry in multiple trauma patients. *Journal of Trauma* 1994; **36**: 313–316.
127. Rush BF, Sori AJ, Murphy TF, Smith S, Flanagan JJJr, Machiedo GW. Endotoxemia and bacteremia during hemorrhagic shock. *Annals of Surgery* 1988; **207**, 549–554.
128. Ryan CM, Yarmush ML, Burke JF, Tompkins RG. Increased gut permeability early after burns correlates with the extent of burn injury. *Critical Care Medicine* 1992; **20**: 1508–1512.
129. Salzman AL, Menconi MJ, Unno N, Ezzell RM, Casey DM, Gonzalez PK, Fink MP. Nitric oxide dilates tight junctions and depletes ATP in cultured Caco-2BBe intestinal epithelial monolayers. *American Journal of Physiology* 1995; **268**: G361–G373.
130. Salzman AL, Wang H, Wollert PS, VanderMeer TJ, Compton CC, Denenberg AG, Fink MP. Endotoxin-induced ileal mucosal hyperpermeability in pigs: role of tissue acidosis. *American Journal of Physiology* 1994; **266**: G633–G646.
131. Schmidt A, Heid HW, Schafer S, Nuber UA, Zimbelmann R, Franke WW. Desmosomes and cytoskeletal architecture in epithelial differentiation: cell type-specific plaque components and intermediate filament anchorage. *European Journal of Cell Biology* 1994; **65**: 229–245.
132. Sedman PC, Macfie J, Sagar P, Mitchell CJ, May J, Mancey-Jones B, Johnstone D. The prevalence of gut translocation in humans. *Gastroenterology* 1994; **107**: 643–649.
133. Shepherd AP, Kiel JW. A model of countercurrent shunting of oxygen in the intestinal villus. *American Journal of Physiology* 1992; **262**: H1136–H1142.
134. Siesjo BK, Bendek G, Koide T, Westergerg E, Wieloch T. Influence of acidosis on lipid peroxidation in brain tissues *in vitro*. *Journal of Cerebral Blood Flow and Metabolism* 1985; **5**: 253–258.
135. Silverman HJ, Tuma P. Gastric tonometry in patients with sepsis. Effects of dobutamine infusions and packed red blood cell transfusions. *Chest* 1992; **102**: 184–188.
136. Spitz J, Hecht G, Taveras M, Aoys E, Alverdy J. The effect of dexamethasone administration on rat intestinal permeability: to role of bacterial adherence. *Gastroenterology* 1994; **106**: 35–41.

137. Stark ME, Szurszewski JH. Role of nitric oxide in gastrointestinal and hepatic function and disease. *Gastroenterology* 1992; **103**: 1928–1949.
138. Steeb GD, Wilson MA, Garrison RN. Pentoxyfylline preserves small-intestine microvascular blood flow during bacteremia. *Surgery* 1992; **112**: 756–764.
139. Stuehr DJ, Nathan CF. Nitric oxide: a macrophage produce responsible for cytostasis and respiratory inhibition in tumor target cells. *Journal of Experimental Medicine* 1989; **169**: 1543–1555.
140. Suleymanlar G, Zhou HZ, McCormack M, Elkins N, Kucera R, Reiss OK, Shapiro JI. Mechanism of impaired energy metabolism during acidosis: role of oxidative metabolism. *American Journal of Physiology* 1992; **262**: H1818–H1822.
141. Sundqvist T, Liu SM. Hydrogen peroxide stimulates endocytosis in cultured bovine aortic endothelial cells. *Acta Physiologica Scandinavica* 1993; **149**: 127–131.
142. Tepperman BL, Brown JF, Korolkiewicz R, Whittle BJR. Nitric oxide synthase activity, viability and cyclic GMP levels in rat colonic epithelial cells: effect of endotoxin challenge. *Journal of Pharmacology and Experimental Therapeutics* 1994; **271**: 1477–1482.
143. Tepperman BL, Brown JF, Whittle BJR. Nitric oxide synthase induction and intestinal cell viability in rats. *American Journal of Physiology* 1993; **265**: G214–G218.
144. Trier JS. Structure and function of intestinal M cells. *Gastroenterology Clinics of North America* 1991; **20**: 531–547.
145. Trivedi B, Danforth WH. Effect of pH on the kinetics of frog muscle phosphofructokinase. *Journal of Biological Chemistry* 1966; **241**: 4110–4114.
146. Unno N, Menconi MJ, Salzman AL, Smith M, Hagen S, Ge Y, Ezzell RM, Fink MP. Hyperpermeability and ATP depletion induced by chronic hypoxia or glycolytic inhibition in Caco-2_{BBe} monolayers. *American Journal of Physiology* (in press).
147. Unno N, Menconi MJ, Smith M, Fink MP. Nitric oxide mediates interferon-gamma-induced hyperpermeability in cultured human intestinal epithelial monolayers. *Critical Care Medicine* 1995; **23**: 1170–1176.
148. van der Waaij D, Berghuis-deVries JM, Lekkerkerk-van der Wees JEC. Colonization resistance of the digestive tract in conventional and antibiotic treated mice. *Journal of Hygiene* 1971; **69**: 405–411.
149. van Deventer SJM, tenCate JW, Tytgat GNJ. Intestinal endotoxemia: clinical significance. *Gastroenterology* 1988; **94**: 823–831.
150. van Goor H, Rosman C, Grond J, Kooi K, Wübbels GH, Bleichrodt RP. Translocation of bacteria and endotoxin in organ donors. *Archives of Surgery* 1994; **129**: 1063–1066.
151. van Lanschot JJB, Mealy K, Wilmore DW. The effects of tumor necrosis factor on intestinal structure and metabolism. *Annals of Surgery* 1990; **212**: 663–670.
152. VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Critical Care Medicine* 1995; **23**: 1217–1226.
153. Vary TC, Siegel JH, Nakatani T, Sato T, Aoyama H. Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. *American Journal of Physiology* 1986; **250**: E634–E640.
154. Vodovotz Y, Kwon NS, Pospischil M, Manning J, Paik J, Nathan C. Inactivation of nitric oxide synthase after prolonged incubation of mouse macrophages with IFN-γ and bacterial lipopolysaccharide. *Journal of Immunology* 1994; **152**: 4110–4118.
155. Walker WA, Cornell R, Davenport LM, Isselbacher KJ. Macromolecular absorption: mechanism of horseradish peroxidase uptake and transport in adult and neonatal rat intestine. *Journal of Cell Biology* 1972; **54**: 195–205.
156. Ward SM, Xue C, Shuttleworth CW, Bredt DS, Snyder SH. NADPH diaphorase and nitric oxide synthase colocalization in enteric neurons of canine proximal colon. *American Journal of Physiology* 1992; **263**: G277–G284.
157. Watanabe H, Kuhne W, Spahr R, Schwartz P, Piper HM. Macromolecule permeability of coronary and aortic endothelial monolayers under energy depletion. *American Journal of Physiology* 1991; **260**: H1344–H1352.
158. Wells CL, Jechorek RP, Erlandsen SL. Evidence for the translocation of *Enterococcus faecalis* across the mouse intestinal tract. *Journal of Infectious Disease* 1990; **162**: 82–90.
159. Wells CL, Jechorek RP, Erlandsen SL. Inhibitory effect of bile on bacterial invasion of enterocytes: possible mechanism for increased translocation associated with obstructive jaundice. *Critical Care Medicine* 1995; **23**: 301–307.
160. Welsh MJ, Shasby DM, Husted RM. Oxidants increase paracellular permeability in a cultured epithelial cell line. *Journal of Clinical Investigation* 1985; **76**: 1155–1168.
161. Whitworth PW, Cryer HM, Garrison RN, Baumgarten TE, Harris PD. Hypoperfusion of the intestinal microcirculation with increased cardiac output during live *Escherichia coli* sepsis in rats. *Circulatory Shock* 1989; **27**: 111–122.
162. Williams G, Brown T, Becker L, Prager M, Giroir BP. Cytokine-induce expression of nitric oxide synthase in C2C12 skeletal muscle myocytes. *American Journal of Physiology* 1994; **267**: R1021–R1025.
163. Wilmore DW, Goodwin CW, Aulick LH, Powanda MC, Mason AD, Pruitt BA. Effect of injury and infection on visceral metabolism and circulation. *Annals of Surgery* 1980; **192**: 491–504.
164. Wilson J, Winter M, Shasby DM. Oxidants, ATP depletion, and endothelial permeability to macromolecules. *Blood* 1990; **76**: 2578–2582.
165. Winchurch RA, Thupari JN, Munster AM. Endotoxemia in burn patients: levels of circulating endotoxin are related to burn size. *Surgery* 1987; **102**: 808–812.
166. Wolburg H, Rohlmann A. Structure-function relationships in gap junctions. *International Review of Cytology* 1995; **157**: 315–373.
167. Xu D, Lu Q, Guillory D, Cruz N, Berg R, Deitch EA. Mechanisms of endotoxin-induced intestinal injury in a hyperdynamic model of sepsis. *Journal of Trauma* 1993; **34**: 676–683.
168. Yoshimura K, Nakagawa S, Koyama S, Kobayashi T, Homma T. Leukotriene B_4 induces lung injury in the rabbit: Role of neutrophils and the effect of indomethacin. *Journal of Applied Physiology* 1993; **74**: 2174–2179.
169. Zeller WP, The SM, Sweet M, Goto M, Gottschalk ME, Hurley RM, Filkens JP, Hoffman C. Altered glucose transporter mRNA abundance in a rat model of endotoxic shock. *Biochemical Biophysical Research Communications* 1991; **176**: 535–540.
170. Ziegler TR, Smith RJ, O'Dwyer ST, Demling RH, Wilmore DW. Increased intestinal permeability associated with infection in burn patients. *Archives of Surgery* 1988; **123**: 1313–1319.

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Mechanisms of acute renal failure

C. J. LOTE, L. HARPER AND C. O. S. SAVAGE

Acute renal failure can be defined as an abrupt decline in renal function with a decrease in glomerular filtration rate (GFR) resulting in the retention of nitrogenous waste products. Acute renal failure has conventionally been classified as (a) prerenal failure, denoting a disorder in the systemic circulation that causes renal hypoperfusion. Implicit in the prerenal classification is that the correction of the underlying circulatory disturbance (e.g. by improvement in cardiac function or repletion of volume) restores the GFR. However, prerenal failure is often followed by transition to (b) intrinsic renal failure, where correction of the circulatory impairment does not restore the normal GFR. Intrinsic renal failure generally includes tubular necrosis. (c) Postrenal failure (obstructive) is a third possibility.

Some patients with acute renal failure have oliguria (conventionally defined as a urine output of less than 400 ml day^{-1}), but others do not. In fact, patients with acute renal failure can be divided approximately equally into oliguric and non-oliguric. The pathogenetic factors appear to be identical in both types but in general are less severe in non-oliguric acute renal failure.

Three abnormalities of renal function are present in intrinsic acute renal failure. These are (1) intratubular obstruction, (2) backleak of glomerular filtrate through damaged tubular epithelium, and (3) a primary reduction of GFR as a consequence of the release of vasoactive substances, which alter pressure, flow and filtration coefficient (k_f) in the glomerular capillaries.

The kidneys have an enormous blood supply. They receive 20–25 % of the cardiac output, but account for only 0.5 % of the body weight. The renal blood supply is typically around 400 ml 100 g^{-1} min^{-1} compared with about 70 ml 100 g^{-1} min^{-1} for heart and liver. The kidneys also have a very high oxygen consumption, but because of the high blood flow, the arteriovenous oxygen difference across the kidney is small. $P\text{O}_2$ decreases from 95 mm Hg in the renal artery, to a value of about 70 mm Hg in the renal venous blood. In view of this it may seem surprising that renal ischaemia and acute renal failure are such major problems.

In this article we examine those features of the renal physiology which contribute to the (intrinsic) failure of the kidney after renal hypoperfusion. What happens when the renal circulation is compromised, and how does this lead on to intrinsic renal failure? How can an organ which has a huge blood supply, and a very low oxygen extraction, be so susceptible to ischaemia and hypoxia? The answers are complex; they necessitate an understanding of renal haemodynamics and their control, and of the role of the kidney in circumstances in which the effective circulating volume is reduced.

Renal blood supply

One of the first aspects of renal haemodynamics which physiology students learn is the concept of "autoregulation" (fig. 1). When mean renal arterial pressure is varied over the range 90–200 mm Hg, there is little effect on renal blood flow. The mechanism of this is still controversial; the most likely explanation is that there is a myogenic response, whereby the increased wall tension in the afferent arterioles, brought about by an increase in perfusion pressure, causes automatic contraction of the smooth muscle fibres in the vessel wall, thereby increasing the resistance to flow and so keeping the flow constant in spite of the increase in perfusion pressure. The alternative hypothesis is that a tubulo-glomerular feedback (TGF) mechanism is responsible for autoregulation, whereby increased perfusion pressure will increase filtration, increasing the tubular fluid delivery to the macula densa which then releases a factor or factors which causes vasconstriction. Which of these hypotheses is correct is debatable [33].

However, the concept of autoregulation can be very misleading. Notwithstanding autoregulation, when effective circulating volume decreases there is a reduction in renal blood flow. This should not be surprising. It has been known for a very long time that stimulation of the renal nerves causes loss of colour from the kidney surface as a result of renal vasoconstriction [4], and this renal vasoconstriction occurs at relatively low levels of renal nerve activity (2 Hz), with increases in both afferent and efferent arteriolar resistance. Higher levels of stimulation (5–20 Hz) primarily constrict the afferent arterioles [18].

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Key words

Kidney, failure. Kidney, blood flow. Kidney, metabolism.

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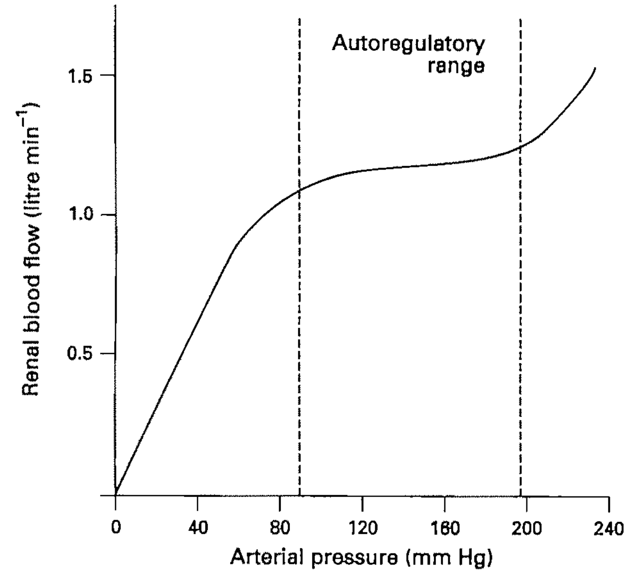

Figure 1 The autoregulation of renal blood flow. In the "autoregulatory range" (90–200 mm Hg), a change in the mean renal perfusion pressure has little effect on the blood flow. The graph can be misleading, since *in vivo* the kidneys do not respond passively to changes in blood pressure, but are active components of blood pressure regulation. (From ref. [22].)

As mentioned above, the kidneys, relative to their size, receive a huge fraction of the cardiac output (20–25 %), and in times of stress, sympathetically mediated renal vasconstriction can shunt the large blood flow to extrarenal sites. Thus, whereas the autoregulation diagram gives the impression that the kidneys *react* to changes in blood pressure, the reality is that the kidneys play a major role in the *regulation* of blood pressure, and many authors have emphasized that renal blood flow decreases whenever cardiac output is decreased secondary to volume depletion [24], although there is continuing controversy over the magnitude of the decrease.

Thus systemic blood pressure is not a good guide to the adequacy of renal perfusion. If there is a decrease in the effective circulating volume (for whatever reason), there may be catastrophic underperfusion of the kidneys, even though blood pressure is in the "autoregulatory" range; this is by virtue of the fact that it may be intense renal vasoconstriction that is the reason for the blood pressure being maintained. So, overt hypotension is not a prerequisite for the development of acute renal failure, and modest reductions in cardiac output, with maintained blood pressure, can imply substantial renal ischaemia. But, if the kidneys normally have such a large blood supply, why does ischaemic damage occur so readily?

The renal medullary blood supply

The function of the renal medulla is to maintain a high osmolality (produced by solute transport out of the ascending limb of the loop of Henle), in order to allow the tubular fluid to be concentrated by the osmotic abstraction of water from the collecting ducts. This function demands a specialized blood supply; conventional capillaries traversing the renal medulla would instantaneously dissipate the corticomedullary solute gradient. The specialization is the countercurrent arrangement of the vasa recta (fig. 2), which minimizes washout of solutes from the medullary interstitium. However, for vasa recta countercurrent exchange to operate, it is essential that the haematocrit of the blood entering the vasa recta should be low. If it were not, then the osmotic removal of water from the descending vasa recta (fig. 3) would dramatically increase the blood viscosity. Even with a low haematocrit, there is a considerable increase in viscosity due to the increase in intravascular protein concentration brought about by the countercurrent exchange of water. Furthermore, since the blood entering the descending vasa recta is derived from efferent arterioles and is unlikely to have gained any tubular fluid reabsorbate, the

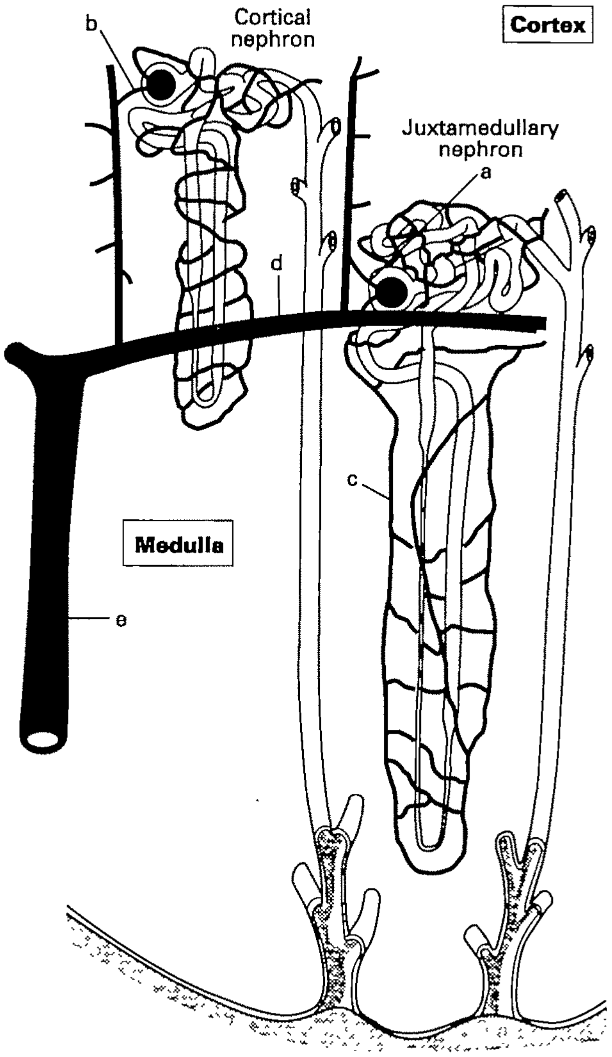

Figure 2 Diagram to show the anatomical arrangement of the blood supply to the nephrons. For clarity, venules and veins are omitted. A typical juxtamedullary nephron (15 % of the total) and cortical nephron (85 % of the total) are shown on the right and left respectively. Note that the afferent arterioles of the juxtamedullary nephrons (labelled a) leave the interlobular artery at a retrograde angle, whereas the afferent arteriole of the cortical nephron (labelled b) leaves at a shallow angle. Thus, plasma skimming is more likely in the blood to the juxtamedullary nephron, the efferent arteriole of which supplies the vasa recta (c). Only two nephrons are shown complete. Other afferent arterioles are shown, but not the glomeruli. Other labels: arcuate artery (d) running along corticomedullary boundary. Interlobar artery (e).

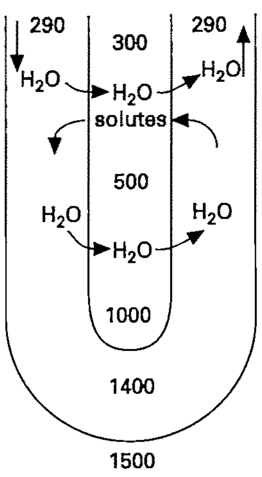

Figure 3 Countercurrent exchange of water and solutes in the vasa recta. The osmotic gradient in the renal medulla/papilla, set up by extrusion of sodium and chloride from the thick ascending limb of the loop of Henle (not shown), causes solute to enter the descending vasa recta limb (on left), and water to leave, so that there is equilibration with any level of the interstitium. The removal of water from the descending limb raises the plasma protein concentration and concentrates the erythrocytes. Hence a low haemocrit at the beginning of the vasa recta is necessary. (From ref. [22].)

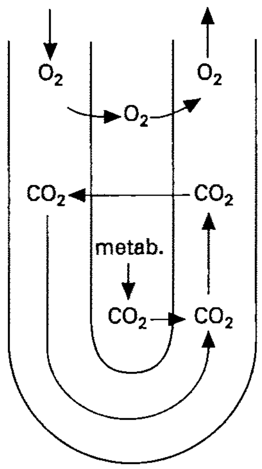

Figure 4 Countercurrent exchange of oxygen and carbon dioxide in the vasa recta. The diffusion gradient causes oxygen to leave the descending limb and enter the ascending limb, and vice versa for carbon dioxide. Thus the cells deep in the renal medulla/papilla have a hypoxic and hypercapnic environment. (From ref. [22].)

increased viscosity which will have occurred because of glomerular filtration will still be present in the blood entering the vasa recta.

Most measurements of the haematocrit for the blood entering the inner medullary descending vasa recta give values of about 10% [31]. Why is the haematocrit low in the blood entering the vasa recta? The vasa recta are derived from the efferent arterioles of juxtamedullary nephrons, which are the first nephrons to be supplied by the interlobular arteries (fig. 2). There are some obvious differences between the afferent arterioles of juxtamedullary glomeruli when compared with other glomeruli. The afferent arterioles of the juxtamedullary glomeruli, as they branch from the interlobular arteries, do so at right angles or even at retrograde angles [21]. This leads to plasma skimming [2] so the blood which enters the branch vessel (the afferent arteriole) is likely to have a reduced haematocrit. The important point is that the volume of the blood flow into the medulla is not a good indication of the adequacy of the blood supply for tissue metabolism, because of the low haematocrit and hence low oxygen-carrying capacity of the blood. This situation is then further exacerbated by the countercurrent exchange process in the vasa recta, because oxygen and carbon dioxide take part in this countercurrent exchange (fig. 4) [22]. Consequently, the cells of the renal papilla live in a remarkably hostile environment, with high (and labile) osmolality, poor oxygen delivery, and poor carbon dioxide removal. The degree of hypoxia in this part of the kidney is shown in figure 5.

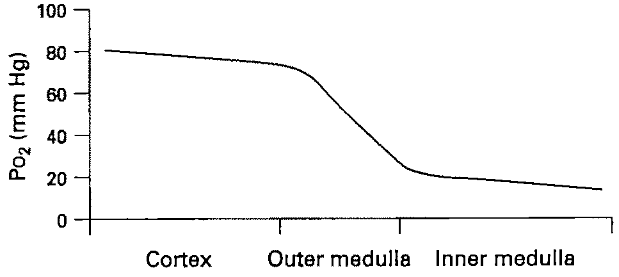

Figure 5 The Po_2 (mm Hg) from cortex to medulla, showing the dramatic decreases in Po_2 in the inner medulla as a result of countercurrent exchange of oxygen in vasa recta (as shown in fig. 4).

Thus, although the blood flow rates in the renal medulla and papilla are well within the range found in other metabolically active tissues, the low haematocrit and countercurrent exchange of oxygen lead to very low oxygen availability for the papillary cells.

The renal cortical blood supply

The obvious specialization of the cortical blood supply is the fact that there are two capillary beds in series—the glomerular capillaries and the peritubular capillaries. These are linked by the efferent arterioles which thus constitute portal vessels. There are a number of reports that the Pco_2 is high in the renal cortex (e.g. ref. [9]) and it is suggested that this is because countercurrent exchange can occur in the cortical peritubular capillaries, as it does in medullary vasa recta. However, others have found typical tissue values of Pco_2 in the renal cortex [25], and at the time of writing the question of whether renal cortical tissue Pco_2 is atypically high remains unresolved.

The kidneys as guardians of the effective circulating volume

Renal tissue damage will occur when the renal blood supply is insufficient to sustain the metabolic demands of the cells. Hypoxia limits ATP production, and hence impairs those cells dependent on oxidative metabolism [35]. Changes of cellular pH as a consequence of oxygen deprivation can also impair glycolytic (anaerobic) metabolism [27].

Although it might be supposed that the renal sites which have the highest oxidative metabolism (i.e. proximal tubule), would be the ones most affected by

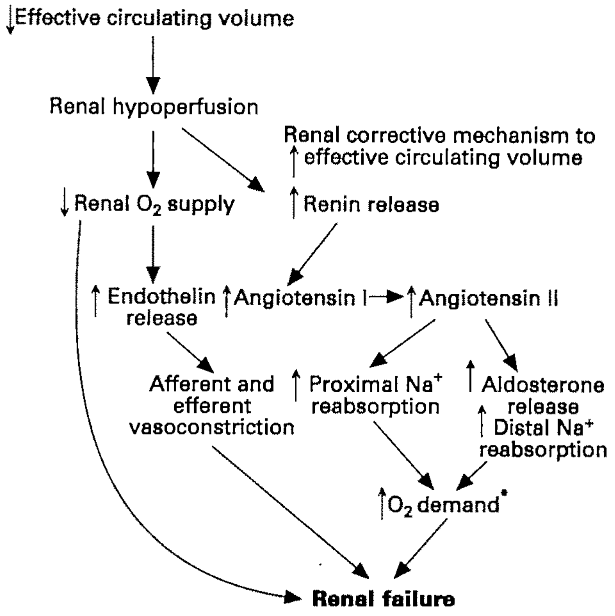
↓Effective circulating volume
Renal hypoperfusion
Renal corrective mechanism to ↑ effective circulating volume
↓Renal O₂ supply
↑Renin release
↑ Endothelin release
↑Angiotensin I
↑Angiotensin II
Afferent and efferent vasoconstriction
↑ Proximal Na⁺ reabsorption
↑ Aldosterone release
↑ Distal Na⁺ reabsorption
↑O₂ demand*
Renal failure

Figure 6 The typical sequence of events leading to acute ischaemic renal failure. * Na^+ transport by the Na^+/K^+ ATPase accounts for 80% + of renal oxygen consumption.

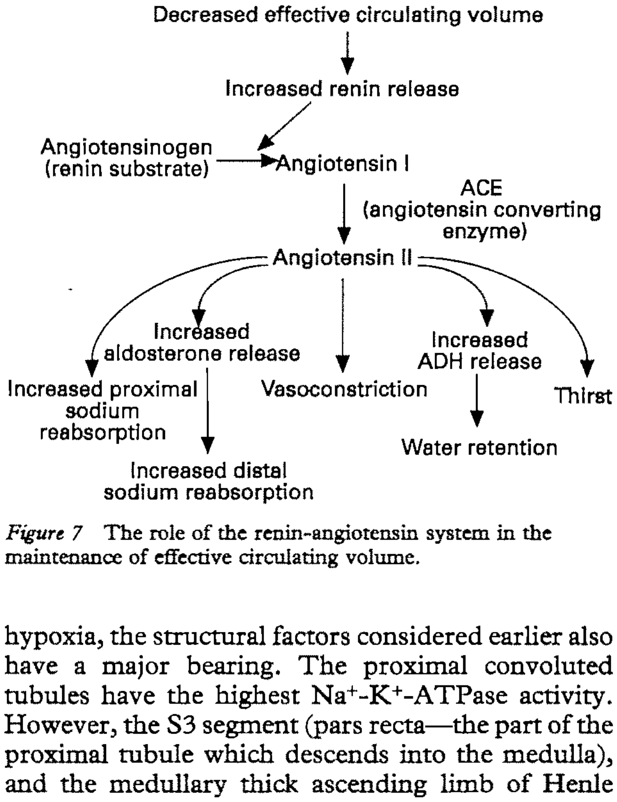
Decreased effective circulating volume
Increased renin release
Angiotensinogen (renin substrate)
Angiotensin I
ACE (angiotensin converting enzyme)
Angiotensin II
Increased aldosterone release
Increased ADH release
Increased proximal sodium reabsorption
Vasoconstriction
Thirst
Water retention
Increased distal sodium reabsorption

Figure 7 The role of the renin-angiotensin system in the maintenance of effective circulating volume.

hypoxia, the structural factors considered earlier also have a major bearing. The proximal convoluted tubules have the highest Na^+-K^+-ATPase activity. However, the S3 segment (pars recta—the part of the proximal tubule which descends into the medulla), and the medullary thick ascending limb of Henle (both of which have considerable glycolytic capability) are the sites commonly damaged in ischaemic acute renal failure. These sites, while having important transport roles, are also affected by the oxygen shunting in the vasa recta.

Eighty percent of the renal oxygen consumption is utilized to drive the Na^+-K^+-ATPase on the basal side of the tubule cells which is responsible for nephron sodium reabsorption. Many of the other transport processes along the nephron (e.g. glucose reabsorption, amino acid reabsorption, organic acid secretion) are secondary active processes which are driven by the gradient for sodium entry across the apical membrane. Thus, there would be almost no transport across the tubular cells without Na^+-K^+-ATPase activity. However, there are differences in the properties of the Na^+-K^+-ATPase in different nephron segments. For example, the Na^+-K^+-ATPase is 10–30 times more sensitive to ouabain in the collecting tubule (where the final adjustments to sodium excretion occur) than in the proximal tubule [8]. These differences raise the possibility of different control mechanisms over Na^+-K^+-ATPase activity in different nephron segments. This is discussed in more detail below.

As the foregoing has demonstrated, decreases in effective circulating volume lead to a reduction in renal perfusion, and this threatens the kidneys by further reducing the blood supply to sites where it is only just adequate. However, renal hypoperfusion is a signal of hypovolaemia to the kidneys, and brings into play renal correcting mechanisms to increase sodium and water reabsorption, and hence restore effective circulating volume. But for the kidneys to do this, their oxygen consumption must increase. This sequence of events, potentially leading to renal failure, is shown in figure 6.

Renal hypoperfusion is a powerful stimulus to renin release from the renin-containing granular cells of the afferent arteriole. Three main signals mediate this release.

(1) *The afferent arteriolar "baroreceptor" mechanism.* Decreased wall tension in the afferent arterioles as a consequence of decreased renal perfusion, increases renin release.

(2) *The sympathetic innervation to the granular cells.* Systemic baroreceptor reflexes activated by decreased effective circulating volume (and consequent decreased blood pressure) increase the activity in these nerves, increasing renin release.

(3) *The macula densa.* This is a sensor in the early part of the distal tubule (which is in close proximity to the afferent arteriole), which responds to decreased sodium chloride delivery into the distal tubule by increasing renin release. Sodium chloride delivery to this site decreases when there is a decrease in effective circulating volume, as a consequence of several factors, including decreased GFR, and decreased peritubular capillary hydrostatic pressure which leads to increased proximal tubular reabsorption.

The consequences of increased renin release are shown in figure 7 where it can be seen that the effects of increased angiotensin II production serve to increase effective circulating volume. Incidentally, the renal vasoconstriction induced by angiotensin II is predominantly of the efferent arteriole, but the renal vasoconstrictor effect of angiotensin II is anyway markedly attenuated because angiotensin II is a powerful stimulus for the production of vasodilator prostaglandins (see blow). Thus, the vasoconstrictor effect of angiotensin II is primarily, (though not exclusively) systemic rather than renal.

However, another vasoconstrictor peptide, endothelin-1 may act more locally. Its release and the tissue sensitivity to its effects are both enhanced by hypoxia [17]. Endothelin-1 mediates afferent and efferent arteriolar vasoconstriction, reducing renal plasma flow and glomerular filtration rate (fig. 6).

The sequence of events shown in figure 6 might seem to indicate that renal failure would be inevitable whenever there is a decrease in effective circulating volume, and this is obviously not the case. This is because there are intrinsic renal protective mechanisms. To a large extent, these are dependent on arachidonic acid metabolism.

Protective role of renal arachidonic acid metabolism

There are many excellent recent reviews of renal arachidonic acid metabolism [23]. This section will therefore focus on those aspects of arachidonate metabolism which have particular relevance to renal function in hypoxia and ischaemia.

The availability of free arachidonic acid as a substrate for the enzymes which convert it to active products, is very limited, since most of the esterified arachidonic acid which is converted to free arachidonic acid by phospholipase A2 is normally re-esterified. This requires ATP, and hence is oxygen dependent, so hypoxia and ischaemia are powerful stimuli for renal prostaglandin synthesis. An alternative or additional possibility is that a hypoxia-induced increase in intracellular (cytosolic) Ca^{2+} concentration enhances phospholipase A2 activity [23].

Free arachidonic acid can be metabolized via three routes, as shown in figure 8. The major cyclo-oxygenase products have renal tubular and renal vascular actions, both of which are important in the renal response to ischaemia and anoxia. Non-steroidal anti-inflammatory drugs (such as indomethacin) which are cyclo-oxygenase inhibitors, have little or no effect on renal blood flow (RBF) or GFR in healthy subjects, but cause marked decreases in RBF and GFR when the renal circulation is compromised, for example by haemorrhage [6]. This indicates that vasodilator products of the cyclo-oxygenase enzyme (mainly prostaglandin E_2 and prostacyclin PGI_2) play an important role in maintaining blood flow and GFR in these circumstances.

In addition to these haemodynamic vasodilator actions, PGE_2 also reduces sodium reabsorption in the thick ascending limb of the loop of Henle [32] and the collecting duct [19] and hence reduces the oxygen consumption of the cells at these sites [20].

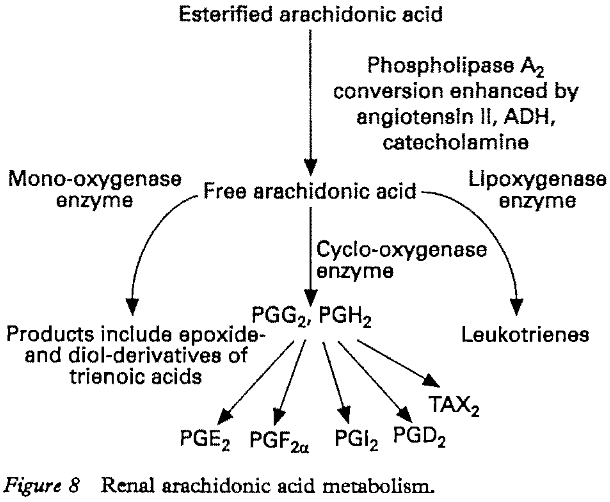
Esterified arachidonic acid
Phospholipase A_2 conversion enhanced by angiotensin II, ADH, catecholamine
Mono-oxygenase enzyme
Free arachidonic acid
Lipoxygenase enzyme
Cyclo-oxygenase enzyme
PGG_2, PGH_2
Products include epoxide- and diol-derivatives of trienoic acids
Leukotrienes
TAX_2
PGE_2
$PGF_{2\alpha}$
PGI_2
PGD_2

Figure 8 Renal arachidonic acid metabolism.

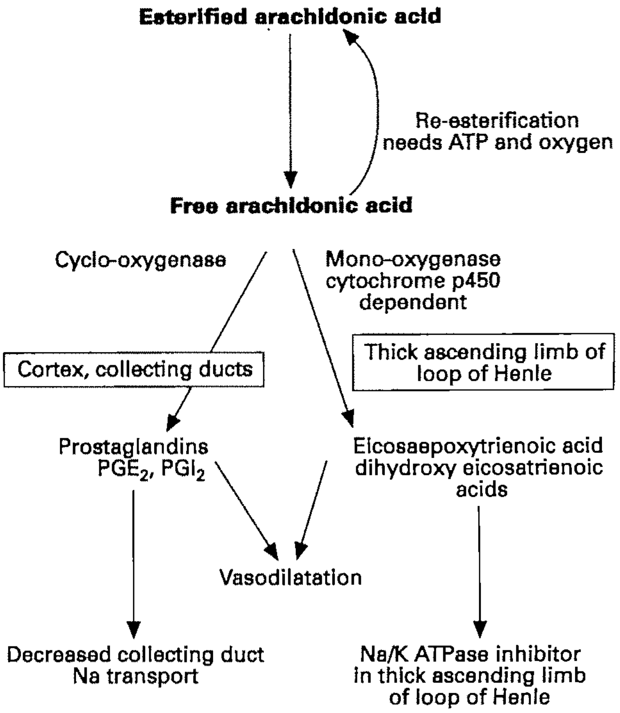
Esterified arachidonic acid
Re-esterification needs ATP and oxygen
Free arachidonic acid
Cyclo-oxygenase
Mono-oxygenase cytochrome p450 dependent
Cortex, collecting ducts
Thick ascending limb of loop of Henle
Prostaglandins PGE_2, PGI_2
Eicosaepoxytrienoic acid dihydroxy eicosatrienoic acids
Vasodilatation
Decreased collecting duct Na transport
Na/K ATPase inhibitor in thick ascending limb of loop of Henle

Figure 9 The renal protective effects of arachidonic acid metabolism.

Products of the cytochrome P450-dependent mono-oxygenase enzyme may also be important in the ischaemic kidney. One product of this enzyme, probably a derivative of 11, 12-dihydroxyeicosatrienoic acid, produced in cells of the thick ascending limb of Henle, is a sodium potassium ATPase inhibitor at this site, and another (5,6-eicosaepoxytrienoic acid) is a vasodilator [5].

The renal protective actions of the arachidonic acid products are summarized in figure 9.

Other protective mechanisms

It was mentioned earlier that there are differences in the control over Na^+-K^+-ATPase activity at different sites in the nephron, and this fact will have been apparent from the foregoing section. However, arachidonic acid products are not the only humoral agents which influence Na^+-K^+-ATPase activity. The effects of aldosterone are predominantly on the activity of Na^+-K^+-ATPase in the collecting tubule, where it acts by inducing the synthesis of new transporter molecules [12]. However this, of course, increases oxygen demand. There are other agents which reduce oxygen demand, important among which are atrial natriuretic peptide and its renal analogue, renal natriuretic peptide (urodilatin) [14, 36] (fig. 10). There are high affinity binding sites for these peptides in the collecting ducts, binding to which leads to an increase in intracellular cGMP, which in turn inhibits ouabain-sensitive oxygen consumption [36] and this is assumed to inhibit sodium transport.

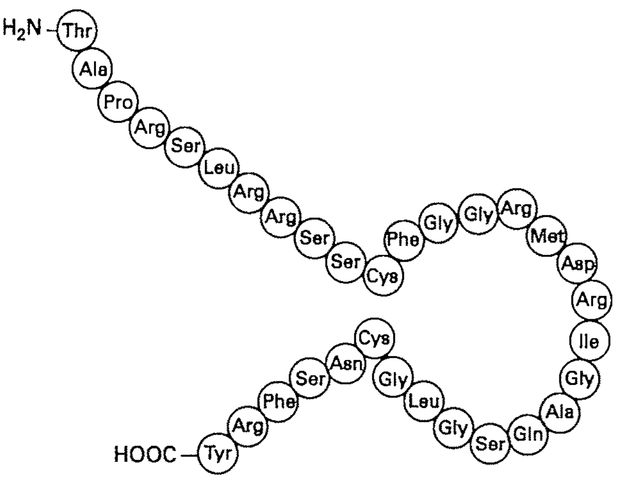

Figure 10 Renal natriuretic peptide (urodilatin). The major circulating form of atrial natriuretic peptide, α-human ANP, is identical except that it does not contain the 4 N-terminal amino acids (Thr, Ala, Pro, Arg).

Recent evidence suggests that atrial natriuretic peptide is primarily a cardiovascular regulator and relatively unimportant for sodium excretion, whereas renal natriuretic peptide is more likely to participate in the intrarenal regulation of sodium excretion [13]. The renal natriuretic peptide is synthesized in the distal cortical nephron, and may be secreted into the cortical peritubular capillaries, or directly into the tubular lumen [36].

Role of endotoxins, inflammatory mediators and nitric oxide in acute renal failure

Sepsis is a common cause of acute renal failure and septicaemia is a common event in patients with acute renal failure, particularly those requiring intensive care. Infective agents may exert their effects by both direct and indirect mechanisms. Many of the indirect effects are mediated through the potent bacterial product, endotoxin or lipopolysaccharide (LPS). LPS may act on many cell types, particularly endothelial cells, monocytes and neutrophils. It can bind directly to, and activate cells via the glycosylphosphoinositol-anchored membrane protein CD14; interactions between LPS and CD14 are facilitated by serum factors including LPS binding protein.

The endothelial cell phenotypic changes induced by LPS are almost identical to those induced by the cytokines TNF and IL-1 [7, 28] and include: (a) the upregulation of cell surface adhesion molecules such as E-selectin, ICAM-1 and VCAM-1 that promote leucocyte adhesion and transmigration; (b) the development of a procoagulant surface through enhanced expression of tissue factor, enhanced release of von Willebrand factor from internal stores in response to agonists (e.g. thrombin), increased secretion of plasminogen activator inhibitor-1 (with subsequent reduced fibrinolytic capacity) and reduced expression of thrombomodulin (with reduced activation of the protein C, protein S pathways); (c) the induction of inflammatory mediator secretion from endothelial cells, including prostacyclin (PGI_2) platelet activating factor (PAF), nitric oxide (NO) and endothelin-1; and (d) the secretion of growth factors, secondary cytokines, leucocyte chemoattractants and enzymes related to matrix degradation.

In addition to its effects on endothelial cells, endotoxin may also activate neutrophils and monocytes, while within the kidney it may induce adhesion molecule upregulation on renal epithelial and mesangial cells. Injection of endotoxin into baboons caused acute renal failure and dramatic upregulation within glomeruli of the adhesion molecule E-selectin (that binds ligands on neutrophils, monocytes and some T-cells) [28]. Accumulated activated neutrophils secrete proteases and free oxygen radicals which damage the glomerular basement membrane and nearby cells. Activated monocytes express tissue factor (favouring coagulation) and secrete further cytokines including IL-1 and TNF that potentiate the effect of endotoxin.

Many of the secondary inflammatory mediators induced by endotoxin can have far reaching effects. Thus, PAF is a product of arachidonic acid metabolism that is released by vascular endothelial cells and which, among its many functions, is a potent platelet activator. The two vasodilators PGI_2 and NO may be released from endothelial cells in response to LPS, while LPS-stimulated monocytes and mesangial cells are a further source of NO [30]. The induction of NO by endotoxin in these cell types differs, reflecting the predominant NO synthase (NOS) enzyme present; NOS generate NO from the terminal guanidino nitrogen of L-arginine. Endothelial NOS is a constitutive enzyme that is dependent on calcium and calmodulin for activity and it continuously produces nmol quantities of NO. Macrophage NOS is not calcium/calmodulin dependent and is induced by endotoxin and certain cytokines such as TNF and IL-1; this induction occurs over hours as it requires new protein synthesis but it leads to sustained production of mmol quantities of NO. Endotoxin and cytokine upregulation of NO from endothelial cells occurs because these factors increase the levels of tetrahydrobiopterin, an essential cofactor, although recently an inducible NOS has been described in endothelial cells also. An inducible NOS is present too in glomerular mesangial cells. NO inhibits platelet aggregation (as does PGI_2) and adhesion to collagen, effects which may be renal protective. However, excess NO levels in sepsis are blamed for the negative inotropic effects on cardiac muscle and for the profound vasodilatation (often resistant to vasopressors) that occurs in septic shock. Nitric oxide has complex interactions with other vasoactive systems—angiotensin II, sympathetic nervous system catecholamines, endothelin I, and prostaglandins; a detailed description of these effects is beyond the scope of this article but they are reviewed in ref. 30.

In parallel with the enhanced NO production, endotoxin may also upregulate the potent constrictor peptide, endothelin [17]. Local endothelin I production may contribute to the renal vasoconstriction that occurs during septic shock since administration of anti-endothelin immunoglobulin directly into the renal artery completely reverses endotoxin-induced renal vasoconstriction.

Prevention of acute renal failure

Prevention of acute renal failure is clearly a better option than treatment. Patients at risk of acute renal failure can be identified and certain simple measures may help to prevent the subsequent development of acute renal failure.

The following conditions predispose to development of acute renal failure:

(1) pre-existing renal impairment
(2) diabetes mellitus (both insulin-dependent and non-insulin dependent)
(3) hypertension and/or vascular disease, particularly renal vascular disease
(4) jaundice
(5) multiple myeloma
(6) age.

The incidence of acute renal failure in the above groups of patients is high after the use of i.v. contrast media, use of nephrotic drugs (e.g. non-steroidal anti-inflammatory drugs, gentamicin, amphotericin) and surgery. Measures that may be taken to reduce the risk of acute renal failure include discontinuation of nephrotoxic agents wherever possible (such as non-steroidal anti-inflammatory drugs) or monitoring levels carefully to avoid toxic concentrations (as with gentamicin).

It is important to eliminate dehydration in "at risk" individuals by evaluating fluid status (if necessary with a central venous catheter) and administering fluid (if necessary i.v. using normal saline in preference to 5% dextrose in patients with renal impairment). Adequate extracellular volume status before major surgery is an excellent preventative measure particularly in the jaundiced patient or those undergoing aortic surgery [3]. Recently, in a prospective study, patients with a mildly elevated creatinine who underwent coronary angiography were hydrated with 0.45% saline before and after angiography. Saline alone significantly reduced the risk of renal failure induced by radiocontrast agents compared with saline and frusemide or mannitol [34].

The role of dopamine as a renoprotective agent is controversial. Dopamine is used widely in the dose range 2–5 $\mu g\ kg^{-1}\ min^{-1}$ and is said to act as a renal vasodilator. There is significant overlap in the stimulation of beta-adrenergic and alpha-adrenergic receptors even at these doses. The increased blood flow is probably the result of the inotropic effects of dopamine and can be reproduced by other non-dopamineric inotropes. In a randomized double-blind trial [11], dopamine and dobutamine were compared for their ability to improve renal function. Dopamine acted as a diuretic and did not improve creatinine clearance. Dobutamine, a non-dopaminergic inotrope, improved creatinine clearance without a change in urine output [11].

The diuresis commonly seen after administration of dopamine is probably the result of a direct tubular effect. However, dopamine impairs the important tubuloglomerular feedback mechanism which may adversely affect the oxygen supply and demand balance, possibly promoting the development of acute tubular necrosis [10]. Dopamine is commonly used to prevent acute tubular necrosis. The evidence supporting this is poorly controlled and often anecdotal. A recent well designed trial [1] showed no benefit in the prevention of renal dysfunction in well hydrated patients undergoing elective abdominal surgery receiving dopamine [1]. In another controlled study, patients undergoing coronary artery bypass surgery failed to derive any benefit from prophylactic dopamine [26]. There is one study in which dopamine protected against radiocontrast-induced renal failure in patients with pre-existing renal impairment; however, no diabetics were included [16].

Mannitol is an osmotic diuretic which if administered prophylactically to patients undergoing surgery can reduce the incidence of acute renal failure. However a recent prospective trial found no additional benefit beyond adequate hydration [15]. The beneficial effects of mannitol are thought to be due to decreased intratubular obstruction and improved renal haemodynamics secondary to an increase in medullary blood flow and cellular protection.

At present there is no acknowledged treatment which reduces duration or mortality of acute renal failure since the advent of dialysis. However, recent animal studies have indicated that atrial natriuretic peptide (ANP) attenuates the severity and/or accelerates the recovery in experimental models of acute renal failure [29]. ANP increases GFR in pathological states, by increasing the glomerular capillary perfusion pressure and has a direct diuretic and natriuretic effect on the distal tubule as described earlier. In a randomized blinded study in humans, ANP appeared to reduce the need for dialysis and increased creatinine clearance when given parenterally to those patients with established intrinsic acute renal failure. There was no improvement in mortality [15]. This study needs to be reproduced in larger trials before definitive conclusions on the use of ANP in acute renal failure can be made.

Conclusions

The structural specialization of the renal circulation is necessary for its function, but some features of the specialization make the kidneys prone to ischaemic and/or hypoxic failure. Most importantly, despite the low oxygen extraction overall, the renal blood supply is not excessive, and indeed is barely adequate in some areas. Excessive reliance on blood pressure measurements (indicating a pressure in the "autoregulatory range") overlooks the fact that the renal blood flow is labile since the kidneys contribute to the regulation of blood pressure.

So, is there an easy way of assessing whether the kidneys are failing after an ischaemic episode? Urinary measurements are a useful indicator. If the effective circulating volume has been reduced the kidneys, if functioning normally, will be maximally reabsorbing sodium and water. Consequently, the urine volume will be small, urine osmolality will be high (e.g. over 800 mosmol/kg H_2O), and the urinary sodium concentration will be low (e.g. less than

25 mmol litre^{-1}). In contrast, if the deceased effective circulating volume has induced renal failure, then urine volume will be small (or there may be no urine produced at all) as a consequence of decreased GFR; but if any urine is produced, it is likely that the urine osmolality will be close to the plasma osmolality (300 mosmol kg^{-1} H_2O) and the urinary sodium will be around 140 mmol litre^{-1}. This is because in acute renal failure, renal concentrating ability is lost. However, there can be considerable overlap between urinary values in prerenal and intrinsic renal failure, and although it is true that most oliguric patients with urine osmolalites below 350 mosmol kg^{-1} H_2O will have intrinsic renal failure, and most with osmolalities over 500 will have prerenal failure, values in between can occur in both conditions.

References

1. Balwin J, Henderson A, Hickman P. Effect of low dose dopamine on renal function after elective major vascular surgery. *Annals of Internal Medicine* 1994; **120**: 744–747.
2. Bankir L, Trinh Trang Tan MM, Grunfeld JP. Measurement of glomerular blood flow in rabbits and rats. Erroneous findings with 15 μm microspheres. *Kidney International* 1979; **15**: 126–133.
3. Barry KG, Mazze RI, Schwartz FD. Prevention of surgical oliguria and renal haemodynamic suppression by sustained hydration. *New England Journal of Medicine* 1964; **270**: 1373–1381.
4. Block MA, Wakim KG, Mann FC. Circulation through kidney during stimulation of the renal nerves. *American Journal of Physiology* 1952; **169**: 659–669.
5. Carroll MA, Schwartzman M, Baba M, Miller MJS, McGiff JC. Renal cytochrome P-450-related arachidonate metabolism in rabbit aortic co-arctation. *American Journal of Physiology*, 1988; **255**: F151–F157.
6. Corwin HL, Bonventre JV. Renal insufficiency associated with nonsteroidal anti-inflammatory agents. *American Journal of Kidney Diseases* 1984; **4**: 147–152.
7. Cotran RS, Pober JS. Effects of cytokines on vascular endothelium: Their role in vascular and immune injury. *Kidney International* 1989; **35**: 969–975.
8. Doucet A, Barlet C. Evidence for differences in the sensitivity to ouabain of Na^+-K^+-ATPase along the nephrons of rabbit kidney. *Journal of Biological Chemistry* 1986; **261**: 993–995.
9. Dubose TD, jr, Caflisch CR, Bidani A. Role of metabolic CO_2 production in the generation of elevated renal cortical pCO_2 *American Journal of Physiology* 1984; **246**: F592–F599.
10. Duke GJ, Bersten AD. Dopamine and renal salvage in the critically ill patient. *Anaesthesia in Intensive Care* 1992; **20**: 277–302.
11. Duke GJ, Briedis JH, Weaver RA. Renal support in critically ill patients: Low dose dopamine or low dose dobutamine? *Critical Care Medicine* 1994; **22**: 1919–1925.
12. El Mernissi G, Doucet A. Specific activity of Na^+-K^+-ATPase after adrenalectomy and hormone replacement along rabbit nephron. *Pflügers Archives* 1984; **402**: 258–263.
13. Goetz KL. Renal natriuretic peptide (urodilatin?) and atriopeptin: Evolving concepts. *American Journal of Physiology* 1991; **261**: F921–F932.
14. Greenwald JE, Needleman P, Wilkins MR, Schreiner GF. Renal synthesis of atriopeptin-like protein in physiology and pathophysiology. *American Journal of Physiology* 1991; **260**: F602–F607.
15. Gubern JM, Sancho JJ, Simo J, Sitges-Serra A. A randomised trial on the effect of mannitol on post-operative renal function in patients with obstructive jaundice. *Surgery* 1988; **103**: 39–44.
16. Hall KA, Wong RW, Hunter GC, Camazine BM, Rappaport WA, Smyth SH, Bull DA, McIntyre KE, Bernhard VM, Misiorowski RC. Contrast induced nephrotoxicity: the effects of vasodilatory therapy. *Journal of Surgical Research* 1992; **53**: 317–320.
17. Haynes WG, Webb DJ. The endothelin family of peptides; local hormones with diverse roles in health and disease? *Clinical Science* 1993; **84**: 485–500.
18. Hermansson K, Larson M, Kallskog O, Wolgast M. Influence of renal nerve activity on arteriolar resistance, ultrafiltration dynamics and fluid reabsorption. *Pflügers Archives* 1981; **389**: 85–90.
19. Holt WF, Lechene C. ADH-PGE_2 interactions in cortical collecting tubule 1. Depression of sodium transport. *American Journal of Physiology* 1981; **241**: F452–F460.
20. Jabs K, Zeidel ML, Silva P. Prostaglandin E_2 inhibits Na^+-K-ATPase activity in the inner medullary collecting duct. *American Journal of Physiology* 1989; **257**: F424–F430.
21. Jamison RL, Kriz W. *Urinary Concentrating Mechanism.* New York; Oxford University Press, 1982: 233–242.
22. Lote CJ. *Principles of Renal Physiology*, 3rd ed. London: Chapman and Hall, 1994.
23. Lote CJ, Haylor J. Eicosanoids in renal function. *Prostaglandins, Leukotrienes and Essential Fatty Acids Reviews* 1989; **36**: 203–217.
24. Madias NE, Donohue FJ, Harrington JT. Postischemic acute renal failure. In: Brenner BM, Lazarus JM, eds. *Acute Renal Failure*, 2nd ed. New York: Churchill Livingstone, 1988: 251–278.
25. Mello Aires Mde, Lopes MJ, Malnic G. PCO_2 in renal cortex. *American Journal Physiology* 1990; **259**: F357–F365.
26. Myles PS, Buckland MR, Schenk NJ, Cannon GB, Langley M, Davis BB. Effect of renal dose dopamine on renal function following cardiac surgery. *Anaesthesia in Intensive Care* 1993; **21**: 56–61.
27. Neely JR, Grotyohann LW. Role of glycolytic products in damage to ischemic myocardium. *Circulation Research* 1984; **55**: 816–824.
28. Pearson JD, May MJ. Regulation of endothelial cell function by cytokines. In: Savage COS, Pearson JD, eds *Immunological Aspects of Vascular Endothelium.* Cambridge: CUP, 1995: 20–42.
29. Rahman SN, Kim GE, Mathew AS, Goldberg CA, Allgen R, Schrier RW, Conger JD. Effects of atrial natriuretic peptide in clinical acute renal failure. *Kidney International* 1994; **45**: 1731–1738.
30. Raij L, Baylis C. Glomerular actions of nitric oxide. *Kidney International* 1995; **48**: 20–32.
31. Rasmussen SN. Effects of osmotic diuresis and water diuresis on intrarenal red cell and plasma volumes in the rat. *Pflügers Archives* 1974; **1**: 1–11.
32. Reeves WB, Molony DA, Andreoli TE. Diluting power of thick limbs of Henle III. Modulation of in vitro diluting power. *American Journal of Physiology* 1988; **255**: F1145–F1154.
33. Steinhausen M, Endlich K, Wiegman DL. Glomerular blood flow. *Kidney International* 1990; **38**: 769–784.
34. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol and frusemide on acute decreases in renal function by radiocontrast agents. *New England Medical Journal* 1994; **331**: 1414–1416.
35. Weinberg JM. The cell biology of ischemic renal injury. *Kidney International* 1991; **39**: 476–500.
36. Zeidel ML, Silva P, Brenner BM, Seifter JL. cGMP mediates effects of atrial peptides on medullary collecting duct cells. *American Journal of Physiology* 1987; **252**: F551–F560.

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Fulminant and late onset hepatic failure

A. E. S. GIMSON

For many years the definition of fulminant hepatic failure, first introduced by Trey and Davidson in 1970, has been used, describing a clinical syndrome of sudden massive hepatocyte dysfunction in the absence of prior liver disease and resulting in hepatic encephalopathy [93]. Although in many series mortality has continued to reach 80%, those that do survive have full functional and structural regeneration without the development of chronic liver disease.

In recent years there has been a renewed debate as to the definition of fulminant hepatic failure [12, 72]. Previous groups have restricted the diagnosis to those with encephalopathy developing between 3, 4 or 6 weeks [7, 9, 33, 41]. The King's College Group has recently proposed a new terminology around the core term acute liver failure. Those patients presenting within 7 days of the onset of jaundice were defined as having hyperacute liver failure, those presenting within 8–28 days of jaundice defined as acute liver failure and those presenting between 29 and 72 days as having subacute liver failure. This definition is of importance as it categorizes groups with different aetiologies and, more importantly, different incidence of the major complication cerebral oedema. This is more common in those with hyperacute or acute liver failure and less common in those with the subacute variety. Similarly, there are differences in prognosis. In hyperacute liver failure with medical management alone the prognosis is relatively good (36% survival) where as in those with subacute liver failure prognosis is poor with only a 14% survival rate. All these studies have concluded that duration from onset of symptoms to encephalopathy is of prime importance in defining different prognostic groups, irrespective of the aetiology, and exemplify the fact that fulminant hepatic failure represents a heterogeneous group of conditions with diverse aetiologies and prognoses. Assessing the aetiology is, therefore, of crucial importance not only because of specific therapy directed to that aetiology but also in predicting subsequent outcome and need for additional nonmedical interventions such as orthotopic liver transplantation.

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Key words

Liver, function. Complications, liver disease. Complications, jaundice. Complications, cerebral oedema.

Aetiology

Fulminant hepatic failure is uncommon and the majority of cases are the result of drug hepatotoxicity or viral hepatitis (table 1).

DRUG HEPATOTOXICITY

Paracetamol hepatotoxicity, the most common cause of fulminant hepatic failure in the United Kingdom, usually occurs after consumption of more than 12 g of the drug. More recently the importance of inadvertent paracetamol hepatotoxicity often taken for an intercurrent illness and without suicidal intent has been stressed. Patients with enzyme induction due to alcohol abuse [61] or the consumption of enzyme-inducing drugs leads to induction of the cytochrome system and increased production of the toxic metabolite [57]. Hepatic metabolism of paracetamol initially occurs via sulphation and glucuronidation. When this metabolic pathway is saturated a cytochrome P450 mechanism may result in the formation of an unstable toxic nucleophilic compound *N*-acetyl-*p*-benzoquinone imine. This compound is detoxified by tissue glutathione and when stores of this are depleted hepatic damage occurs. Prior depletion of tissue glutathione due to oxidant stress or alcohol consumption will also aggravate hepatocyte injury. The antidote *N*-acetylcysteine (NAC) if given within 16 h of the overdose may act as a sulphydryl donor and neutralize the toxic metabolite. Recent evidence from retrospective analyses [47] as well as a prospective randomized controlled trial suggest that patients with significant hepatotoxicity and liver failure may benefit from NAC even when given more than 16 h after the initial overdose. In these important studies reduced organ dysfunction and significantly improved survival were observed [56]. While the mechanism of action of NAC at this later stage is likely to be different from that when given within the first 16 h it is clear that all patients who have taken a significant paracetamol overdose and have evidence of hepatotoxicity should be given a continuous NAC infusion until normalization of markers of hepatocyte damage.

A wide range of other drug toxicities may occur leading to fulminant hepatic failure. Halothane hepatotoxicity is now rare, usually occurring in

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Table 1 Aetiology of fulminant hepatic failure

Viral
  Acute hepatitis A (HAV)
  Acute hepatitis B (HBV) ± hepatitis D co-infection
  Hepatitis D (HDV) superinfection of a chronic HBV carrier
  Hepatitis B reactivation in a chronic HBV carrier
  Acute hepatitis C (HCV) ± other chronic viral carriage
  Acute hepatitis E (HEV)
  Indeterminate viral hepatitis
  Epstein-Barr virus infection, cytomegalovirus, herpes simplex, herpesvirus-6, varicella
Drugs
  Paracetamol (intentional/unintentional; with/without enzyme induction)
  Halothane, isoflurane, enflurane
  Carbon tetrachloride
  Rare idiosyncratic drug reactions: isoniazid, rifampicin, sodium valproate, ketoconazole, erythromycin, sulphonamides, tricyclic antidepressants, propyl thiouracil, FIAU
Others
  Acute fatty liver of pregnancy, pre-eclamptic syndromes
  Wilson's disease
  Autoimmune chronic active hepatitis
  Budd-Chiari syndrome
  Malignancy; non-Hodgkin's lymphoma, metastatic disease
  Heat stroke
  Amanita poisoning
  Circulatory shock
  Reye's syndrome
  Sepsis

females up to 21 days after exposure. Multiple exposures are common but it has been reported after a single anaesthetic. Occasionally there may be other features of drug hypersensitivity including a rash, eosinophilia and liver kidney microsomal antibodies in 25% of cases. A specific antibody against a halothane altered component of hepatocyte membranes suggests that the damage may be immunologically mediated. Hepatotoxicity has been reported on rare occasions following enflurane [104] and isofluorane as well as phenytoin, tricyclic antidepressant drugs and sodium valproate [23]. Recently, the importance of significant hepatotoxicity associated with anti-tuberculous medication has been stressed. In these patients oxidant stress and low tissue glutathione concentration as well as enzyme induction due to fasting or chronic alcohol abuse may also contribute to the likelihood of hepatic dysfunction [65].

VIRAL HEPATITIS

In most series fulminant viral hepatitis is the most common cause of acute liver failure. The reason for the development of liver failure in up to 1% of cases is unclear but presumably includes host factors such as age, as well as the size of the inoculum and perhaps virus strains. Fulminant hepatitis A (HAV) is more common in the elderly [36] and i.v. drug users [1] and the mechanism of the damage remains unclear. The prognosis is relatively good with survival rates of up to 50% with medical treatment alone. Fulminant hepatitis B (HBV) is an important cause of acute liver failure [40, 74], the risk of a fulminant presentation being higher than with HAV, and more common in women or after termination of chemotherapy and immunosuppression in HBV carriers [16]. It may also occur with HBV reactivation, with HBe antigen/HBe antibody seroconversion and when there is associated delta HDV co-infection or super-infection of HBV carriers [34, 44].

Table 2 Investigations in patients with fulminant hepatic failure

Full blood count
Prothrombin time/prothrombin ratio
Serum electrolytes, creatinine and phosphate
Serum bilirubin, albumin, transaminases, alkaline phosphatase, amylase
Serum/urine for toxicological screen
Viral serology
  HAV IgM anti-HAV
  HBV HBsAg, IgM anti-HBc, HBV DNA
  HCV Anti-HCV antibody, HCV mRNA
  HDV IgM anti-HDV
  HEV Anti-HEV antibody
  Serology for CMV, EBV, herpes, etc. and convalescent sera if available.
Serum copper, caeruloplasmin. 24-h urinary copper and penicillamine challenge if appropriate
Autoantibodies/immunoglobulins
Chest x-ray
Ultrasound scan of liver (size, texture, patency of portal/hepatic veins. Spleen size)
Slit-lamp examination for Keyser-Fleischer rings

Hepatitis C (HCV) has been considered only rarely as a cause of acute liver failure, on the basis on anti-HCV serology [43]. In contrast, recent studies have suggested that HCV may account for up to 30% of cases of serologically indeterminate viral hepatitis when HCV mRNA is tested by polymerase chain reaction (PCR). In these studies the importance of multiple viral co-infection has also been stressed. Other viral causes include hepatitis E infection [3, 60], particularly in the Indian subcontinent and rarely Epstein-Barr virus [26], cytomegalovirus [49], herpes simplex [24], varicella [66] and herpesvirus-6 [73]. These cases often occur in immunocompromised individuals.

A long list of rare causes of fulminant hepatic failure account for approximately 5% of the cases but accurate diagnosis is essential (table 2). Liver failure associated with pregnancy may be caused by acute fatty liver of pregnancy or eclamptic syndromes [27, 80, 81]. The Budd-Chiari syndrome [78], disseminated malignancy (in particular non-Hodgkin's lymphoma [102]) and Wilson's disease may also present a fulminant course [8]. The clue is often the presence of hepatosplenomegaly. Reye's syndrome is a further rare cause of acute liver failure but is more common in young children [31]. The cause is unknown but interest has centred on the role of salicylates and the use of these drugs in febrile children is no longer recommended. In such cases the primary lesion of diffuse microvascular fatty change within the liver is different from that observed in most other forms of fulminant hepatic failure. Liver failure has also been recorded in children treated with sodium valproate [103] or tetracycline hepatoxicity and Jamaican vomiting sickness. Recently the development of a diffuse microvascular infiltrate with hepatocellular necrosis has been observed following the use of nucleoside analogues and electron microscopic evidence has pointed to a primary mitochondrial damage [63].

Pathology

The majority of causes of fulminant hepatic failure give rise to a severe and widespread hepatocellular necrosis [52]. This starts in a centrizonal distribution and progresses towards the portal tracts [20]. The degree of associated parenchymal inflammation is highly variable, being more prominent in those with a longer duration of the disease [46]. Canalicular cholestasis may also be apparent but usually is the consequence of sepsis. Initial studies by Horney and Galambos suggested that pathogenesis of fulminant viral hepatitis was due to an ischaemic infarction [50] which, in the context of fulminant hepatitis B, was considered to result from sinusoidal deposition of antigen–antibody complexes following an exaggerated immune response to the hepatitis B virus [40].

Previous suggestions that fulminant hepatic failure may be associated with an impaired hepatic regenerative response have been discounted with the finding of prominent immunostaining for proliferating cell nuclear antigen in surviving hepatocytes [38] and elevated concentrations of hepatocyte growth factor [42].

General management

Management in an intensive care unit is mandatory. Patients require dextrose infusions, prophylaxis for upper gastrointestinal bleeding and close microbiological surveillance. Treatment of the coagulation deficit is needed only if there is overt bleeding.

Attempts at treating fulminant hepatic failure with steroids, insulin and glucagon have been unsuccessful. Other modalities tried have included PGE_1 [11, 88, 89] and interferon with cyclosporin A in patients with fulminant viral hepatitis [101]. These are either of no proved benefit or require further evaluation.

Organ dysfunction and treatment

HEPATIC ENCEPHALOPATHY AND CEREBRAL OEDEMA

During fulminant hepatic failure progressive encephalopathy is subsequently associated with the development of cerebral oedema. The clinical features range from minimal dysphoria and drowsiness in the initial stages to agitation and, later, unresponsiveness to all stimuli in grade 4 encephalopathy (table 3). The rate of progression through these grades varies significantly but is fastest with paracetamol-induced hepatotoxicity. Those patients with grade 4 encephalopathy who develop cerebral oedema have a very high mortality without treatment, compared with those who only develop grade 1 or 2 encephalopathy.

Table 3 Classification of grades of hepatic encephalopathy

Grade 1	Mild confusion, poor concentration occasionally dysphoria. Reversed sleep pattern. When roused fully coherent.
Grade 2	Increasing confusion and disorientation but still rousable and able to be rational.
Grade 3	Sleeping most of the time but can be roused to commands. May be markedly agitated occasionally aggressive.
Grade 4	Not rousable to commands but may or may not be responsive to painful stimuli. Clinical features of cerebral oedema may be apparent during this stage, including hyperventilation, pupillary abnormalities, opisthotonus and extensor plantars. Abnormal respiratory pattern.

The pathogenesis of hepatic encephalopathy in patients with acute liver failure remains unclear. The previous hypotheses centred around hyperammonaemia, changes in the proportional relationship between branch chain and aromatic amino acids, elevation of toxins such as mercaptans and short chain fatty acids with synergistic effects. Unfortunately these have not given consistent results in animal models and, more particularly, the visual evoked responses of animals exposed to these agents do not replicate the responses seen during liver failure. More recent evidence has pointed to the gamma amino butyric acid (GABA) pathway as the major cause of neuronal depression [67]. Although GABA concentrations are not elevated it has been postulated that benzodiazepine-like substances acting via a benzodiazepine receptor closely linked to the GABA receptor may be involved. Basile and colleagues have observed increased concentrations of 1,4-benzodiazepine in brain tissue in both animals and patients with acute liver failure [5, 6]. The relationship between these findings and changes in other neuroexcitatory and depressant pathways including serotinergic, dopaminergic and glutaminergic pathways, remains unclear. The use of a benzodiazepine receptor antagonist such as flumazenil has been associated with minor changes in coma grade for short periods of time but is of little clinical importance [45]. Opioidergic neurotransmission is also altered in animal models of liver failure with increased cerebral levels of Met-Leu encephalin.

Cerebral oedema remains one of the major causes of early mortality in fulminant hepatic failure. During grade 4 encephalopathy it may be present in up to 80 % of cases and is associated with an elevated intracranial pressure, reduction in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRo_2$). As intracranial pressure increases, critical impairment of cerebral oxygenation occurs, with the development of cerebral ischaemia, and tentorial herniation develops in about 25 % of cases. The pathogenesis of this cerebral oedema remains unclear and both cytotoxic and vasogenic hypotheses have been put forward. It is likely that both varieties of cerebral oedema share similar mechanisms at the endothelial level. Electron microscopic studies of brain from patients dying with fulminant hepatic failure have suggested a predominantly cytotoxic origin for the cerebral oedema [55]. This has been suggested to be the result of the presence of inhibitors of neuronal Na/K ATPase [87], although others have not confirmed these findings [75]. An alteration in the blood–brain barrier has also been observed in other animal models. It is most likely that these hypotheses are not mutually exclusive and that the increase in brain water content may initially be cytotoxic associated with glial swelling in cortical grey but not subcortical white matter, and subsequently be associated with alteration in the blood–brain barrier [54].

Cerebral oedema, as in many other pathological situations, is associated with changes in the normal cerebral blood flow autoregulation. Patients with grade 4 encephalopathy and fulminant hepatic failure have a low cerebral blood flow and do not exhibit the usual changes in cerebral blood flow with increases in Pa_{CO_2} [2]. This implies some uncoupling of the usual relationship between cerebral blood flow and $CMRo_2$ [59]. It is also clear that there are pronounced regional differences in cerebral blood flow.

The clinical detection of cerebral oedema is of critical importance [17, 62]. Reliance on such clinical features as systemic hypertension, bradycardia, opisthotonus, abnormal pupillary reflexes and decerebrate posturing only occur late and when therapeutic intervention may be ineffective. The use of computed tomography has variable sensitivity [68] but the most accurate assessment has been the use of an intracranial pressure monitor by the subdural route [18, 29, 62]. Complication rates are acceptably low and it allows the measurement of cerebral perfusion pressure, a critical measure of cerebral oxygen delivery. The increase in intracranial pressure to greater than 20 mm Hg, if untreated, is associated with the subsequent development of tentorial herniation. Transient increases in intracranial pressure may be associated with endotracheal suction, changes in patient position and painful stimuli. Management rests on maintaining normothermia, a head-up position of approximately 20° to the horizontal [25] and the use of i.v. mannitol 0.5 g/kg body weight. Previous trials have demonstrated that dexamethasone and hyperventilation [30] confer no survival benefit but mannitol when given for the above specific indication significantly improves hospital survival [21]. Both mannitol and NAC have been shown to increase cerebral blood flow in patients with grade 4 encephalopathy and this increase in cerebral blood flow is accompanied by an increase in cerebral oxygen extraction [48]. It is important to note that in these circumstances hyperventilation may also result in a decrease in cerebral blood flow usually due to a decrease in cardiac output, and that this decrease in cerebral blood flow may be associated with a reduction in cerebral oxygen extraction [48]. There is no indication that prophylactic mannitol is of benefit and its use should be reserved for specific evidence of intracranial hypertension. Osmotic therapy is ineffective in reducing intracranial pressure in the presence of renal failure [21] unless combined with ultrafiltration of twice the volume of infused mannitol. Other agents including barbiturates may significantly lower intracranial pressure but have profound haemodynamic side effects [35]. It is best considered as a bridge to transplantation to maintain stability while the patient awaits a donor liver.

CARDIOVASCULAR AND PULMONARY DISTURBANCES

Fulminant hepatic failure is associated with profound haemodynamic changes, most particularly, of a marked reduction in systemic vascular resistance. Over 50 % of patients have episodes of hypotension during grade 4 encephalopathy despite an elevated cardiac output, and these abnormalities are of prognostic importance. Despite the elevated cardiac index and arterial oxygen delivery to the tissues (cardiac index × arterial oxygen content, Da_{O_2}) Bihari and colleagues have proposed that an underlying covert tissue hypoxia is present [13]. Hyperlactataemia in the absence of systemic hypotension correlates inversely with systemic vascular resistance implying poor tissue perfusion despite apparently adequate delivery, and changes in the *in vivo* p50, a measure of the position of the oxygen–haemoglobin dissociation curve, are only associated with changes in peripheral oxygen extraction in patients who survive. In cases with an ultimately poor prognosis changes in *in vivo* p50 that might be expected to release more oxygen in the tissues are not associated with any change in oxygen extraction ratio, suggesting a profound disturbance in the control of peripheral circulation and oxygen homeostasis, with poor capillary perfusion [14]. This may result from an interruption to perfusion of some capillaries because of marginated platelets or activated white cells with a reflex arteriolar vasodilatation and luxury perfusion of remaining capillaries [15]. Increases in diffusion distance from capillary lumen to active respiring cells and a reduction in capillary transit time result in impaired oxygen extraction.

These patients exhibit a close relationship between oxygen delivery and oxygen extraction by the tissues. Such supply dependency has been proposed in other states with a high cardiac output/low vascular resistance, although its existence remains controversial. In patients with severe liver disease, use of a peripheral vasodilator such as prostacyclin (PGI_2) is associated with both an increased arterial oxygen delivery and oxygen consumption by the tissues [95]. Similarly NAC results in an increase in both oxygen delivery and oxygen extraction ratio [48]. Such a relationship between oxygen supply and extraction is also found at a tissue level. Changes in cerebral blood flow (using the xenon washout technique) are associated with corresponding changes in $CMRo_2$. Both PGI_2 and NAC increase cerebral oxygen delivery and $CMRo_2$, whereas hyperventilation and vasoconstrictor drugs (despite increasing mean arterial pressure) both reduce $CMRo_2$]96].

These findings carry important consequences for the management of patients with fulminant hepatic failure. Assessment of mean arterial pressure alone is inadequate and arterial oxygen delivery requires careful monitoring. Calculation of arterial oxygen content requires the use of a co-oximeter rather than a calculated arterial oxygen saturation because of significant changes in the position of the oxygen–haemoglobin dissociation curve. Haemodynamic goals of maintaining Da_{O_2} above 700 ml min^{-1} m^2, have been proposed. Other measures to maximize

Da_{O_2} should be attempted and the effect on oxygen extraction assessed.

Pulmonary complications may occur in up to 50% of cases [92]. The majority of cases have a low pulmonary vascular resistance and some increase in alveolar–arterial oxygen difference. In a recent review of cases with liver failure due to paracetamol hepatotoxicity, 33% had severe lung injury (Murray score > 2.5) with hypoxaemia contributing to the death of two patients [4]. Such hypoxaemia may have many causes including aspiration of gastric contents, pulmonary infection or a syndrome of non-cardiogenic pulmonary oedema. Chest radiology significantly underestimates the severity of the pulmonary dysfunction. Endotracheal intubation is usually undertaken when grade 3 encephalopathy occurs and care must be taken to ensure that changes in ventilatory parameters and end-expiratory pressure do not compromise systemic and cerebral haemodynamics.

ELECTROLYTE AND RENAL DYSFUNCTION

Hyponatraemia is a universal finding as a result of water retention and an intracellular sodium shift from inhibition of membrane Na/K ATPase. Saline should not be administered. Hypokalaemia related to the respiratory alkalosis, and hypophosphataemia [28] may also require correction. Hypoglycaemia due to reduced hepatic glycogen stores and hyperinsulinaemia require treatment with continuous glucose administration. Hyperlactataemia and metabolic acidosis occur in up to 30% of cases, predominantly paracetamol induced, and carry a very poor prognosis.

Either acute tubular necrosis or functional renal failure may occur in up to half of all cases [97]. In cases of toxic injury caused by paracetamol, carbon tetrachloride or solvent use, renal impairment may be out of proportion to the hepatic injury. Continuous haemodiafiltration is performed in order to minimize large shifts in solute [98]. Large changes in serum sodium concentration must be avoided particularly at the time of orthotopic liver transplantation, as osmotic demyelination and central pontine myelinolysis may result.

BACTERIAL AND FUNGAL SEPSIS

A wide range of defects in host defences is present. Impaired opsonization, leucocyte chemotaxis [100] and intracellular killing [22] all contribute to a substantial risk of sepsis with up to 80% of patients developing bacterial sepsis and 30% developing fungal infection [83]. The sensitivity and specificity of the usual markers of infection are poor. The majority of infective episodes are related to Gram-positive organisms. Prophylactic antibiotics may have a minor role, although there is no evidence that enteral decontamination is of any benefit [82]. More important is close microbiological surveillance.

Fungal infection is particularly common in cases with prior bacterial sepsis, a low white cell count at presentation and renal failure. Patients require careful monitoring particularly in those proceeding to orthotopic liver transplantation.

DISORDERS OF COAGULATION AND FIBRINOLYSIS

Hepatocellular necrosis results in marked impairment in synthesis of many coagulation factors and their inhibitors, as well as those factors involved in the regulation of fibrinolysis. Only factor VIII concentrations are elevated. In addition to the reduced synthesis, the contribution of increased intravascular consumption of coagulant factors has been controversial for some years, but the recent finding of elevated thrombin–antithrombin III complexes and D-dimer concentrations both indicate intravascular activation of coagulation [58]. In contrast, activation of fibrinolysis is not a significant clinical problem [77].

Progressive thrombocytopenia is universal, associated with the loss of the larger more haemostatically active platelets [85]. Platelets also have reduced aggregation to ADP.

Assessment of prognosis

Improvements in intensive medical management have resulted in a steady increase in survival rates from fulminant hepatic failure. Previous studies have demonstrated that the severity of the liver failure assessed by serial prothrombin times, number and type of organ system failures, and the aetiology of the hepatocellular necrosis are all important [10]. Assessing which patients have the worst prognosis and require consideration for other interventions, including orthotopic liver transplantation, must be undertaken early giving enough time to find an appropriate donor, and at a time when the patient is fit enough to withstand the procedure.

The King's College group has proposed that assessments of prognosis will be different for each aetiology [71]. Paracetamol-induced hepatotoxicity is best assessed by the presence of acidosis (arterial pH < 7.3) and level of prothrombin time [76] (table 4). For all other aetiologies two static variables, age and aetiology, as well as dynamic variables of bilirubin, prothrombin time and time from onset of symptoms to development of encephalopathy are used (table 4). In contrast, Bernau and colleagues proposed that factor V concentrations and age were more discriminatory [10], and a recent study from

Table 4 Criteria for consideration for orthotopic liver transplantation

Paracetamol overdose
  Arterial pH < 7.30
  or all the following
  Prothrombin time > 100 s
  Creatinine > 300 μmol litre^{-1}
  Grade 3 or 4 encephalopathy
  Prothrombin time increasing on day 4
Non-paracetamol overdose
  Any three of the following:
  Aetiology non-A–non-B hepatitis, halothane or drug reaction
  Age < 10 or > 40 years
  Jaundice to encephalopathy
  Serum bilirubin > 300 μmol litre^{-1}
  Prothrombin time > 50 s
  or prothrombin time > 100 s

(Taken from ref. [71])

Table 5 Results of orthotopic liver transplantation for fulminant (FHF) and late onset hepatic failure (LOHF)

	% Grade 3/4			
Author [Ref.]	Patients	FHF/LOHF	Encephalopathy	% Survival
O'Grady [69]	31	16/15	35	61
Vickers [94]	16	16/0	100	56
Schafer [86]	24	24/0	50	58
Emond [32]	19	19/0	84	58
Iwatsuki [53]	42	42/0	64	50
Gallinger [37]	21	9/12	81	72
Rakela [79]	8	8/0	88	63

Japan could not confirm the King's College criteria [91], perhaps reflecting differences in aetiology and medical management.

Each centre needs to develop criteria that can predict outcome as accurately as possible and use these to refer cases for orthotopic liver transplantation. This procedure is usually not performed in patients over the age of 65 years, and does require a satisfactory cardiopulmonary assessment.

Orthotopic liver transplantation

For those patients with the worst prognosis orthotopic liver transplantation remains their only chance of long-term survival. Survival rates of up to 70% have been reported in some series (table 5). Selection of the patient is important [99]. An upper age limit of 65 years is used in some units and the presence of two other organ system dysfunctions used as a contraindication. Reports of significant brain damage after transplantation related to preoperative cerebral ischaemia and cerebral oedema reflects the difficult issue of the significance of changes in cerebral blood flow and perfusion pressure in predicting neurological outcome [68]. Recent studies have demonstrated that survival without neurological deficit may occur even after periods of up to 3 h of low cerebral perfusion pressure presumably because of very low $CMRo_2$. Possibly the use of jugular bulb cannulation and lactate/oxygen concentrations may give better discrimination.

In those cases with potentially reversible liver dysfunction, such as paracetamol hepatotoxicity, the technique of auxiliary partial orthotopic liver transplantation with a hemihepatectomy of donor and recipient, and grafting of the left lobe of the donor only, have theoretical advantages [19]. If satisfactory regeneration of the native liver occurs then immunosuppression can be withdrawn and the graft then atrophies [64].

Artificial liver support

In recent years the use of temporary liver support with perfusion of hepatocyte or hepatoblastoma cell lines encapsulated within hollow fibres has seen a resurgence of interest [84, 90]. Their use remains experimental and no evidence of survival advantage or basis for a "bridge" to transplantation has been reported. Previous techniques including high flux haemofiltration, charcoal haemoperfusion [39, 70] and Amberlite XAD-7 perfusion [51]; all had some problems of bioincompatibility and were clinically ineffective. Indeed, the concept that the major problem in the late stages of fulminant hepatic failure is the result of the failure of the liver to clear "toxins" may be false. Studies demonstrating dramatic improvements in cerebral perfusion pressure, and systemic vascular resistance on exclusion of the liver from the circulation or hepatectomy, suggest that substances released by the necrotic organ may be just as important. Until more efficient biocompatible devices are available, artificial liver support will develop only slowly.

References

1. Akriviadis EA, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. *Annals of Internal Medicine* 1989; **110**: 838–839.
2. Almdal T, Schroeder T, Ranek L. Cerebral blood flow and liver function in patients with encephalopathy due to acute and chronic liver diseases. *Scandinavian Journal of Gastroenterology* 1989; **24**: 299–303.
3. Asher LVS, Innis BL, Shrestha MP, Ticehurst J, Baze WB. Virus-like particles in the liver of a patient with fulminant hepatitis and antibody to hepatitis E virus. *Journal of Medical Virology* 1990; **31**: 229–233.
4. Baudouin SV, Howdle P, O'Grady JG, Webster NR. Acute lung injury in fulminant hepatic failure following paracetamol poisoning. *Thorax* 1995; **50**: 399–402.
5. Basile AS, Pannell L, Jaouni T, Gammal SH, Fales HM, Jones EA, Skolnick P. Brain concentrations of benzodiazepines are elevated in an animal model of hepatic encephalopathy. *Proceedings of National Academy of Science USA* 1990; **87**: 5263–5267.
6. Basile AS, Hughes RD, Harrison PM, Jones EA, Williams R, Skolnick P. Elevated brain concentrations of 1,4-benzodiazepines in fulminant hepatic failure. *New England Journal of Medicine* 1991; **325**: 473–478.
7. Benhamou JP. Fulminant and subfulminant hepatic failure: definition and causes. In: Williams R, Hughes RD, eds. *Acute Liver Failure Improved Understanding and Better Therapy.* London: Mitre Press, 1991; 6–10.
8. Berman DH, Leventhal RI, Gavaler JS, Cadoff EM, Van Thiel DH. Clinical differentiation of fulminant Wilsonian hepatitis from other causes of hepatic failure. *Gastroenterology* 1991; **100**: 1129–1134.
9. Bernuau J, Rueff B, Benhamou J-P. Fulminant and subfulminant liver failure: definitions and causes. *Seminars in Liver Disease* 1986; **6**: 97–106.
10. Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage G, Yvonnet B, Degott C, Bezeaud A, Rueff B, Benhamou JP. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986; **6**: 648–651.
11. Bernuau J, Babany G, Bezeaud A, Benhamou JP. Does prostaglandin E1 (PGE1) prevent further aggravation in severe, or early fulminant, hepatitis? A preliminary open trial (abstract). *Journal of Hepatology* 1989; **9**: S114.

12. Bernuau J, Benhamou JP. Classifying acute liver failure. *Lancet* 1993; **342**: 252.
13. Bihari D, Gimson AES. Waterson M, Williams R. Tissue hypoxia in fulminant hepatic failure. *Critical Care Medicine* 1985; **3**: 1034–1039.
14. Bihari DJ, Gimson AES, Williams R. Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. *Seminars in Liver Disease* 1986; **6**: 119–128.
15. Bihari D, Wendon J. Tissue hypoxia in fulminant hepatic failure. In: Williams R, Hughes RD, eds. *Acute Liver Failure: Improved Understanding and Better Therapy*. London: Mitre Press, 1991: 4244.
16. Bird GLA, Smith H, Portmann B, Alexander GJM, Williams R. Acute liver decompensation on withdrawal of cytotoxic chemotherapy and immunosuppressive therapy in hepatitis B carriers. *Quarterly Journal of Medicine* 1989; **73**: 895–902.
17. Blei AT. Cerebral edema and intracranial hypertension in acute liver failure: distinct aspects of the same problem. *Hepatology* 1991; **13**: 376–379.
18. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993; **341**: 157–158.
19. Boudjema K, Cherqui D, Jaeck D, Chenard-Neu M-P. Auxiliary liver transplantation for fulminant and subfulminant hepatic failure. *Transplantation* 1995; **59**: 218–223.
20. Boyer JL, Klatskin G. Pattern of necrosis in acute viral hepatitis. Prognostic value of bridging (subacute hepatic necrosis). *New England Journal of Medicine* 1970; **12**: 1063–1071.
21. Canalese J, Gimson AES, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut* 1982; **23**: 625–629.
22. Canalese J, Gove C, Gimson AES, Wilkinson SP, Wadle EN, Williams R. Reticuloendothelial system and hepatocyte function in fulminant hepatic failure. *Gut* 1982; **23**: 265–269.
23. Carson JL, Strom BL, Duff A, Gupta A, Shaw M, Lundin FE, Das K. Acute liver disease associated with erythromycins, sulphonamides and tetracyclines. *Annals of Internal Medicine* 1993; **119**: 576–583.
24. Connor RW, Lorts G, Gilbert DN. Lethal herpes simplex virus type 1 hepatitis in a normal adult. *Gastroenterology* 1979; **76**: 590–594.
25. Davenport A, Will EJ, Davison AM. Effect of posture on intracranial pressure and cerebral perfusion in patients with fulminant hepatic and renal failure after acetaminophen self-poisoning. *Critical Care Medicine* 1980; **18**: 286–289.
26. Davies MH, Morgan-Capner P, Portmann B, Wilkinson SP, Williams R. A fatal case of Epstein-Barr virus infection with jaundice and renal failure. *Postgraduate Medical Journal* 1980; **56**: 794–795.
27. Davies MH, Wilkinson SP, Hanid MA, Portmann B, Brudenell JM, Newton JR, Williams R. Acute liver disease with encephalopathy and renal failure in late pregnancy and the early puerperium. A study of fourteen patients. *British Journal of Obstetrics and Gynaecology* 1980; **87**: 1005–1014.
28. Dawson DJ, Babbs C, Warnes TW, Neary RH. Hypophosphatemia in acute liver failure. *British Medical Journal* 1987; **295**: 1312–1313.
29. Donovan JP, Shaw BW jr, Langnas AN, Sorrell MF. Brain water and acute liver failure: the emerging role of intracranial pressure monitoring. *Hepatology* 1992; **16**: 267–268.
30. Ede RJ, Gimson AES, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *Journal of Hepatology* 1986; **2**: 43–51.
31. Ede RJ, Williams R. Reyes syndrome in adults. *British Medical Journal* 1988; **296**: 517.
32. Emond JC, Aran PP, Whitington PF, Broelsch CE, Baker AL. Liver transplantation in the management of fulminant hepatic failure. *Gastroenterology* 1989; **96**: 1583–1588.
33. European Association for the Study of the Liver. Randomised trial of steroid therapy in acute liver failure. *Gut* 1979; **20**: 620–623.
34. Feray C, Gigou M, Samuel D, Reyes G, Bernuau J, Reynes M, Bismuth H, Brechot C. Hepatitis C virus RNA and hepatitis B virus DNA in serum and liver of patients with fulminant hepatitis. *Gastroenterology* 1993; **104**: 549–555.
35. Forbes A, Alexander GJ, O'Grady JG, Keays R, Gullan R, Dawling S, Williams R. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology* 1989; **10**: 306–310.
36. Forbes A, Williams R. Increasing age—an important adverse prognostic factor in hepatitis A virus infection. *Journal of the Royal College of Physicians of London* 1988; **22**: 237–239.
37. Gallinger S, Greig PD, Levy G, Blendis LM, Roberts EA, Superina RA, Taylor BR, Strasberg SM, Phillips MJ, Langer B. Liver transplantation for acute and subacute fulminant hepatic failure. *Transplantation Proceedings* 1989; **21**: 2435–2438.
38. Gerber MA, Thung SN, Shen S, Stromeyer FW, Ishak KG. Phenotypic characterization of hepatic proliferation. Antigenic expression of proliferating epithelial cells in fetal liver, massive hepatic necrosis and nodular transformation of the liver. *American Journal of Pathology* 1983; **110**: 70–74.
39. Gimson AES, Braude S, Mellon P, Canalese J, Williams R. Earlier charcoal haemoperfusion in fulminant hepatic failure. *Lancet* 1982; **ii**: 681–683.
40. Gimson AES, Tedder RS, White YS, Eddleston ALWF, Williams R. Serological markers in fulminant hepatitis B. *Gut* 1983; **24**: 615–617.
41. Gimson AES, O'Grady J, Ede R, Portmann B, Williams R. late-onset hepatic failure: clinical, serological and histological features. *Hepatology* 1986; **6**: 228–294.
42. Gohda E, Tsubouchi H, Nakayama H, Hirono S, Arakaki N, Yamamoto I, Hashimoto S, Daikuhara Y. Human hepatocyte growth factor in blood of patients with fulminant hepatic failure: basic aspects. *Digestive Diseases and Sciences* 1991; **36**: 785–790.
43. Gordon FD, Anastopoulos H, Khettry U, Loda M, Jenkins RL, Lewis WD, Trey C. Hepatitis C infection: a rare cause of fulminant hepatic failure. *American Journal of Gastroenterology* 1995; **90**: 117–120.
44. Govindarajan S, Chin KP, Redeker AG, Peters RL. Fulminant B viral hepatitis: role of delta agent. *Gastroenterology* 1984; **86**: 1417–1420.
45. Grimm G, Ferenci P, Katzenschlager R, Madl C, Schneeweiss B, Laggner AN, Lenz K, Gangl A. Improvement of hepatic encephalopathy treated with flumanzenil. *Lancet* 1991; **2**: 1392–1394.
46. Hanau C, Munoz SJ, Rubin R. Histopathological heterogeneity in fulminant hepatic failure. *Hepatology* 1995; **21**: 345–351.
47. Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Late N-acetylcysteine administration improves outcome for patients developing paracetamol-induced fulminant hepatic failure. *Lancet* 1990; **i**: 1572–1573.
48. Harrison PM, Wendon JA, Gimson AES, Alexander GJM, Williams R. Improvement by N-acetylcysteine of haemodynamics and oxygen transport in fulminant hepatic failure. *New England Journal of Medicine* 1991; **324**: 1852–1857.
49. Henson DE, Crimley PM, Strano AJ. Postnatal cytomegalovirus hepatitis: an autopsy and liver biopsy study. *Human Pathology* 1974; **5**: 93–103.
50. Horney JT, Galambos JT. The liver during and after fulminant hepatitis. *Gastroenterology* 1977; **73**: 639–645.
51. Hughes R, Williams R. Clinical experience with charcoal and resin hemoperfusion. *Seminars in Liver Disease* 1986; **6**: 164–173.
52. Ishak KG. Viral hepatitis: the morphologic spectrum. In: Gall EA, Mostofi FK, eds. *The Liver. International Academy of Pathology Monographs No 13*. Baltimore: Williams and Wilkins, 1973: 218–268.
53. Iwatsuki S, Stieber AC, Marsh JW, Tzakis AG, Todo S, Koneru B, Makowka L, Gordon RD, Starzl TE. Liver transplantation for fulminant hepatic failure. *Transplantation Proceedings* 1989; **21**: 2431–2434.
54. Joo F. A unifying concept on the pathogenesis of brain oedemas. *Neuropathology and Applied Neurobiology* 1990; **13**: 161–176.
55. Kato M, Hughes RD, Keays RT, Williams R. Electron microscopic study of brain capillaries in cerebral edema from fulminant hepatic failure. *Hepatology* 1992; **15**: 1060–1066.
56. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *British Medical Journal* 1991; **303**: 1026–1029.

57. Kumar S, Rex DK. Failure of physicians to recognize acetaminophen hepatotoxicity in chronic alcoholics. *Archives of Internal Medicine* 1991; **151**: 1189–1191.
58. Langley PG, Forbes A, Hughes RD, Williams R. Thrombin-antithrombin III complex in fulminant hepatic failure: evidence for disseminated intravascular coagulation and relationship to outcome. *European Journal of Clinical Investigation* 1990; **20**: 627–631.
59. Larsen FS, Knudsen GM, Paulson OB, Vilstrup H. Cerebral blood flow autoregulation is absent in rats with thioacetamide-induced hepatic failure. *Journal of Hepatology* 1994; **21**: 491–495.
60. Liang TJ, Jeffers L, Reddy RK, Hasegawa K, Rimon N, Wands JR, Ben-Porath E. Fulminant or subfulminant non-A, non-B viral hepatitis: the role of hepatitis C and E viruses. *Gastroenterology* 1993; **104**: 556–562.
61. Licht H, Seeff LB, Zimmerman HJ. Apparent potentiation of acetaminophen hepatotoxicity by alcohol. *Annals of Internal Medicine* 1980; **92**: 511.
62. Lidofsky SD, Bass NM, Prager MC, Washington DE, Read AE, Wright TL, Ascher NL, Roberts JP, Scharschmidt BF, Lake JR. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology* 1992; **16**: 1–7.
63. McKenzie R, Fried MW, Sallie R, Conjeevaram H, Di Bisceglie AM, Park Y, Savarese B, Kleiner D, Tsokos M, Luciano C. Hepatic failure and lactic acidosis due to Fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *New England Journal of Medicine* 1995; **333**: 1099–1105.
64. Metselaar HJ, Hesselink EJ, de Rave S, ten Kate FJ, Lameris JS, Groenland TH, Reuvers CB, Weimar W, Terpstra OT, Schalm SW. Recovery of failing liver after auxiliary heterotopic liver transplantation. *Lancet* 1990; **335**: 1156–1157.
65. Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. *Lancet* 1995; **345**: 555–556.
66. Morishita K, Kodo H, Asano S, Fujii H, Miwa S. Fulminant varicella hepatitis following bone marrow transplantation. *Journal of the American Medical Association* 1985; **253**: 511.
67. Mullen KD, Martin JV, Mendelson WB, Bassett ML, Jones EA. Could an endogenous benzodiazepine ligand contribute to hepatic encephalopathy? *Lancet* 1988; **i**: 457–459.
68. Munoz SJ, Robinson M, Northrup B, Bell R, Moritz M, Jarrell B, Martin P, Maddrey WC. Elevated intracranial pressure and tomography of the brain in fulminant hepatic failure. *Hepatology* 1991; **13s**: 209–212.
69. O'Grady JG, Alexander GJM, Thick M, Potter D, Calne RY, Williams R. Outcome of liver transplantation in the aetiological and clinical variants of acute liver failure. *Quarterly Journal of Medicine* 1988; **69**: 817–824.
70. O'Grady J, Gimson AES, O'Brien C, Pucknell A, Hughes RD, Williams R. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. *Gastroenterology* 1988; **94**: 1186–1192.
71. O'Grady JG, Alexander GJM, Hallyar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439–445.
72. O'Grady JG, Schalm SW, Williams R. Acute liver failure; redefining the syndrome. *Lancet* 1993; **342**: 273–275.
73. Osano Y, Yoshikawa T, Suga S, Yazaki T, Kondo K, Yamanishi K. Fatal fulminant hepatitis in an infant with human herpes virus-6 infection. *Lancet* 1991; **335**: 862–863.
74. Papaevangelou G, Tassopoulos N, Roumeliotou-Karayannis A, Richardson C. Aetiology of fulminant viral hepatitis in Greece. *Hepatology* 1984; **4**: 369–372.
75. Pappas S, Ferenci P, Jones EA. Evidence against the hypothesis that cerebral oedema in FHF is due to decreased neural Na-K ATPase activity. *Hepatology* 1983; **3**: 848 (Abstract).
76. Pereira LMMB, Langley PG, Hayllar KM, Tredger JM, Williams R. Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol induced fulminant hepatic failure: relation to other prognostic indicators. *Gut* 1992; **33**: 98–102.
77. Pernambuco R, Langley PG, Hughes R, Izumi S, Williams R. Activation of the fibrinolytic system in patients with fulminant liver failure. *Hepatology* 1993; **18**: 1350–1356.
78. Powell-Jackson PR, Ede RJ, Williams R. Budd-Chiari syndrome presenting as fulminant hepatic failure. *Gut* 1986; **27**: 1101–1105.
79. Rakela J, Perkins JD, Gross JB jr, Hayes DH, Plevak DJ, Krom RA, Ludwig J. Acute hepatic failure: the emerging role of orthotopic liver transplantation. *Mayo Clinic Proceedings* 1989; **64**: 424–428.
80. Riely CA, Latham PS, Romero R, Duffy TP. Acute fatty liver of pregnancy: a reassessment based on observations in nine patients. *Annals of Internal Medicine* 1987; **106**: 703–706.
81. Rolfes DB, Ishak KG. Acute fatty liver of pregnancy: a clinicopathologic study of 35 cases. *Hepatology* 1985; **5**: 1149–1158.
82. Rolando N, Gimson AES, Wade J, Philpott-Howard J, Casewell M, Williams R. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. *Hepatology* 1993; **17**: 196–201.
83. Roland N, Harvey F, Brahan J, Philpott-Howard J, Gimson AES, Fagan E, Williams R. Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. *Hepatology* 1990; **11**: 49–53.
84. Rozga J, Williams F, Ro MS, Neuzil DF, Giorgio TD, Backfisch G, Moscioni AD, Hakim R, Demetriou AA. Development of a bioartificial liver; properties and function of a hollow fibre module inoculated with liver cells. *Hepatology* 1993; **17**: 258–265.
85. Rubin MH, Weston MJ, Bullock G, Roberts J, Langley PG, White YS, Williams R. Abnormal platelet function and ultrastructure in fulminant hepatic failure. *Quarterly Journal of Medicine* 1977; **183**: 339–352.
86. Schafer DF, Shaw BW. Fulminant hepatic failure and orthotopic liver transplantation. *Seminars in Liver Disease* 1989; **9**: 189–194.
87. Seda HMW, Hughes RD, Gove C, Williams R. Reduced brain Na-K ATPase activity by serum from patients with fulminant hepatic failure. *Hepatology* 1984; **4**: 74–79.
88. Sheiner P, Sinclair S, Greig P, Logan A, Blendis LM, Levy G. A randomized controlled trial of prostaglandin E_2 (PGE_2) in the treatment of fulminant hepatic failure. *Hepatology* 1992; **16** (Suppl): S114 (abstract).
89. Sinclair SB, Greig PD, Blendis LM, Abecassis M, Roberts EA, Phillips MJ, Cameron R, Levy GA. Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E: a preliminary report. *Journal of Clinical Investigation* 1989; **84**: 1063–1069.
90. Sussman NI, Gislason GT, Conlin CA, Kelly JH. The Hepatix extracorporeal liver assist device: initial clinical experience. *Artificial Organs* 1994; **18**: 390–396.
91. Takahashi Y, Kumada H, Shimizu M, Tanikawa K, Kumashiro R, Omato M. A multicentre study on the prognosis of fulminant viral hepatitis: Early prediction for liver transplantation. *Hepatology* 1994; **9**: 1065–1071.
92. Trewby PN, Warren R, Contini S, Crosbie WA, Wilkinson SP, Laws JW, Williams R. Incidence and pathophysiology of pulmonary edema in fulminant hepatic failure. *Gastroenterology* 1978; **74**: 859–865.
93. Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds. *Progress in Liver Diseases*. Vol. III. New York: Grune & Stratton, 1970: 282–298.
94. Vickers C, Neuberger J, Buckels J, McMaster P, Elias E. Transplantation of the liver in adults and children with fulminant hepatic failure. *Journal of Hepatology* 1986; **7**: 143–150.
95. Wendon JA, Gimson AE, Potter D. Oxygen uptake and delivery in fulminant hepatic failure. *Care of the Critically Ill* 1989; **5**: 55–59.
96. Wendon JA, Harrison PM, Keays R, Gimson AES, Alexander GJM, Williams R. Effects of vasopressor agents and epoprostenol on systemic hemodynamics and oxygen transport in patients with fulminant hepatic failure. *Hepatology* 1992; **15**: 1067–1071.
97. Wilkinson SP, Blendis LM, Williams R. Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *British Medical Journal* 1974; **1**: 186–189.
98. Wilkinson SP, Weston MJ, Parsons V, Williams R. Dialysis in the treatment of renal failure in patients with liver disease. *Clinical Nephrology* 1977; **8**: 287–292.
99. Williams R, Wendon J. Indications for orthotopic liver

transplantation in fulminant hepatic failure. *Hepatology* 1994; **20**: 5S–10S.

100. Wyke RJ, Rajkovic IA, Eddleston ALWF, Williams R. Defective opsonisation and complement deficiency in serum from patients with fulminant hepatic failure. *Gut* 1981; **21**: 643–649.
101. Yoshiba M, Sekiyama K, Inoue K, Fujita R. Interferon and cyclosporin A in the treatment of fulminant viral hepatitis. *Journal of Gastroenterology* 1995; **30**: 67–73.
102. Zafrani ES, Leclercq B, Vernant JP, Pinaudeau Y, Chomette G, Dhumeaux D. Massive blastic infiltration of the liver: a cause of fulminant hepatic failure. *Hepatology* 1983; **3**: 428–432.
103. Zimmerman HJ, Ishak KG. Valproate-induced hepatic injury. Analysis of 23 fatal cases. *Hepatology* 1982; **2**: 591–597.
104. Zimmerman H. Even enflurane (Editorial). *Hepatology* 1991; **13**: 1251–1253.

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New approaches to acute lung injury

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The lung responds to acute injury of diverse aetiology via a series of common pathways. The pathological changes caused by a variety of toxic and infectious agents evolve over time from endothelial and epithelial injury to alveolar consolidation and finally to fibroblast proliferation and collagen deposition. Widespread acute injury to the lung produces *diffuse alveolar damage* [33], a well characterized anatomical entity that forms the basis of the protean clinical picture of acute respiratory failure. This clinical picture has been identified in the past by a host of terms, creating some confusion. Recently, a panel of experts clarified the definition of acute lung injury [4]. The terms acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are proposed to describe the continuum of a syndrome of primary respiratory failure, characterized by the acute onset of dyspnoea, hypoxaemia and bilateral consolidation on the chest radiograph (table 1). ALI is considered to be the early stage of ARDS, with milder abnormalities of respiratory function, and it may subsequently evolve into the more severe and more easily diagnosed syndrome of ARDS. The major reason to define ALI is to facilitate experimental and clinical investigation of the early stages of ARDS, in order to improve the early recognition and treatment of this syndrome [4].

Aetiology of ALI and ARDS

There are many known aetiological factors of ARDS. Although little information exists regarding the causes of ALI itself, it seems likely that the aetiologies causing ARDS also cause ALI [4]. The common aetiologies of these syndromes are summarized in table 2. Rather than listing all the known causes, we have emphasized two main aetiological groups, separating causes that arise within the lung from those arising outside the lung. The subsequent anatomical and physiological pattern of lung injury evolves via common pathways, and respiratory failure dominates the clinical presentation. Co-existing acute lung disease may at times cloud the acute onset of respiratory failure; nosocomial pneumonia in particular is both a frequent cause and complication of ALI and presents a diagnostic challenge. It is currently accepted that a syndrome of ALI can develop in patients with co-existing lung disease [4]; at times [52] certain lung pathology, such as interstitial lung disease, pulmonary embolism, invasive carcinoma and *Pneumocystis carinii* pneumonia are excluded from clinical trials of ARDS since they would probably increase the mortality or alter the host's response to ARDS. The incidence of each individual aetiological factor varies widely according with the ICU population under study. In general, medical intensive care units most often treat patients with ALI caused by infectious pneumonia, often with pre-existing chronic lung disease, while surgical intensive care units treat ALI after trauma, burns and abdominal sepsis.

Regardless of whether the primary aetiology originates within or outside the lung, a systemic inflammatory response accompanies and may determine the progression of ALI (table 3). Chemotaxis and activation of leucocytes lead to the release of cytotoxic free radicals and cytokines such as tumour necrosis factor and the interleukins [12]. The expression of leucocyte adhesion molecules and proteases [14] contributes to epithelial and endothelial injury. A number of homeostatic systems are activated: the complement and kinin systems, the coagulation cascade, the cyclo-oxygenase and leukotriene pathways and the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway. The systemic inflammatory process contributing to acute lung injury is complex. We will highlight a few recent and significant findings.

Complete inhibition of local fibrinolysis has been demonstrated in the broncho-alveolar lavage fluid of patients with ARDS but not in the fluid of patients with other forms of acute respiratory failure [7]. The sites of early fibrin and fibronectin deposition in alveoli correlate with the sites of formation of hyaline membranes, the anatomical hallmark of ARDS [33], and the subsequent location of fibrosis and collagen deposition.

Increased local production of NO by inducible NO synthase during sepsis may impair local hypoxic pulmonary vasoconstriction (HPV), impair ventilation to perfusion matching and reduce arterial oxygen tension [54]. In contrast, when low concentrations of NO gas are administered by inhalation, (see section on supportive therapy), NO primarily reaches ventilated alveoli, augments their perfusion and enhances ventilation to perfusion matching,

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Key words

Lung, damage. Complications, acute respiratory distress syndrome. Complications, barotrauma. Pharmacology, nitric oxide. Airway, pressure.

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Table 1 The definition of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) according to the American-European Consensus Conference of ARDS [4]

(1) Acute onset of respiratory distress
(2) Hypoxaemia:
  ALI: $Pa_{O_2}/FI_{O_2} \leqslant 300$ mm Hg
  ARDS: $Pa_{O_2}/FI_{O_2} \leqslant 200$ mm Hg
(3) Bilateral consolidation of chest radiograph
(4) Absence of clinical findings of cardiogenic pulmonary oedema

Table 2 Aetiologies of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). (Aetiologies specific for ALI have not been investigated separately. Since ALI and ARDS are believed to form an anatomical and clinical continuum, the aetiologies of ARDS are extended to ALI)

(1) *Direct lung injury*
  Aspiration pneumonitis
  Other pneumonitis: oxygen, smoke inhalation, radiation, bleomycin
  Infectious pneumonia, community acquired and nosocomial
  Trauma: lung contusion, penetrating chest injury
  Near-drowning
  Fat embolism
(2) *Distant injury*
  Inflammation, necrosis, infection (sepsis syndrome)
  Multiple trauma, burns
  Shock, hypoperfusion
  Acute pancreatitis
  Transfusion-associated lung injury (TRALI)

increasing the arterial oxygen tension [47]. Regional inhibition of NO synthesis may also occur in the sepsis syndrome, promoting vasoconstriction, platelet aggregation and thrombosis; the biological production and effects of NO are widespread and both inhibition and induction of NO synthesis may occur simultaneously in different organ systems at varying times during systemic inflammation [35].

Activation of the cyclo-oxygenase pathway may increase the synthesis of vasoconstrictor prostaglandins (e.g. thromboxane A_2) resulting in pulmonary hypertension, oedema and increased bronchial reactivity. Clinical use of a cyclo-oxygenase inhibitor in patients with ARDS and the sepsis syndrome is currently being investigated [3].

Pathophysiology of ALI and ARDS

ANATOMY

The pathological evolution of ALI and ARDS in animal models has been separated into two discrete phases: an exudative and a proliferative phase. In humans, however, this sequence is not well separated temporally, and exudative and fibrotic regions of the lung often overlap as disease progresses. After the initial acute epithelial and endothelial injury, alveolar oedema, haemorrhage and fibrin deposition occur in the lung, along with a diffuse interstitial inflammatory cell infiltrate (fig. 1). Alveolar exudation is widespread despite a low hydrostatic pressure in the pulmonary vessels: injury rather than an elevated pressure promotes oedema during early ALI. As hyaline membranes progressively line the alveolar spaces, alveolar consolidation results. These anatomical phenomena form the basis for the physiological events of hypoxaemia and reduced compliance. They also justify the logic of the beneficial effect of positive pressure ventilation in promoting alveolar recruitment and, at the same time, explain the exquisite susceptibility of the injured alveolar space to the additional noxious stresses of mechanical ventilation [15]. Early pulmonary vascular lesions include haemorrhage and the formation of microthrombi in capillaries and small pulmonary arteries; later, medial hyperthrophy and intimal fibrosis occur, and eventually large portions of the pulmonary vascular bed may become obliterated [58]. As the syndrome progresses, fibroblast proliferation becomes prominent. Peribronchial and interstitial fibrosis, with variable degrees of chronic inflammation, are characteristic. Fibrosis is at times exceptionally severe (honeycomb lung) and their intensity appears to correlate with a poor prognosis [33].

PHYSIOLOGY

Arterial hypoxaemia and a low lung compliance are the clinical hallmarks of ALI. Alveolar collapse causes hypoxaemia by impairing the matching of ventilation to perfusion. The pulmonary circulation

Table 3 Summary of the complex pathogenesis of acute lung injury/acute respiratory distress syndrome. [Detailed descriptions can be found in refs 7, 12, 14, 54, 58]

Aetiological condition
within or outside the lung: aspiration, trauma, sepsis, etc.
⇓
Initiation of the inflammatory response
dead tissue, endotoxin, bacteria
(1) *Cellular component*
  neutrophils, macrophages, lymphocytes, platelets
  ⇓
  leucocyte activation: release of cytokines, free radicals, adhesion molecules, proteases leading to endothelial and epithelial injury.
(2) *Humoral component*

⇓ *coagulation cascade:*	⇓ *cyclo-oxygenase pathway:*	⇓ *complement system:*	⇓ *nitric oxide*	
			inhibition:	*induction:*
inhibition of fibrinolysis	(thromboxanes) vasoconstriction, platelet aggregation, broncho-constriction	cytotoxicity	platelet aggregation, leucocyte migration, vascular permeability	systemic hypotension, local vasodilatation and venous admixture

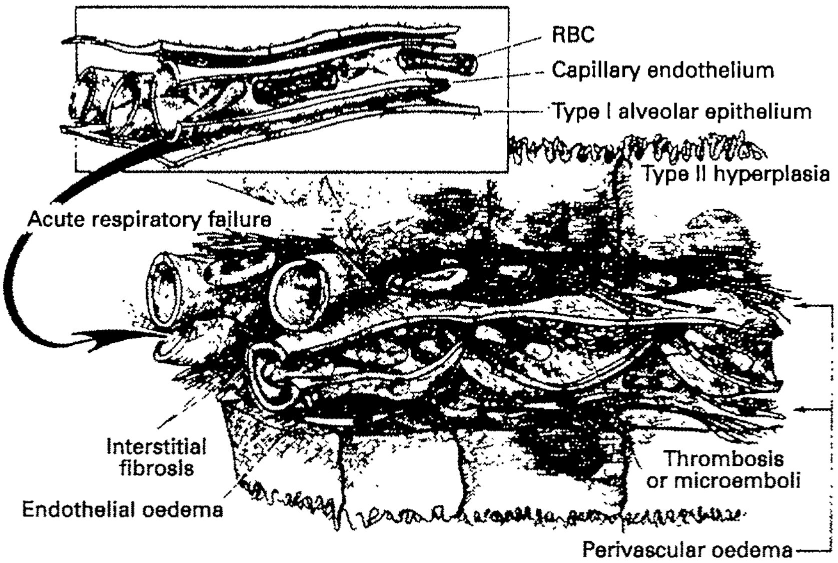

Figure 1 Diagram of the alveolar and vascular components of acute lung injury. (Reproduced with permission from Zapol and colleagues [59].)

normally responds to hypoxaemia by locally constricting blood vessels supplying poorly ventilated alveoli, thereby diverting venous blood flow to well ventilated alveoli. This response, termed hypoxic pulmonary vasoconstriction (HPV), is a homeostatic response required to preserve an adequate arterial oxygen tension. Unfortunately, the combination of HPV, release of vasoconstrictor mediators and down-regulation of the production of vasodilators such as NO and prostacyclin may enhance pulmonary hypertension, which fosters the formation of pulmonary oedema and increases the afterload of the right ventricle. Severe pulmonary hypertension is associated with a high mortality [61]. Vasoconstriction, vascular occlusion and alveolar overdistension by positive pressure ventilation can create lung regions with a high ventilation to perfusion ratio and markedly increase the ventilatory dead space of patients with established ARDS. This augments the ventilatory requirements and increases the risk of alveolar damage due to mechanical forces.

During ARDS, the compliance of the lung is initially decreased by alveolar oedema and collapse, and subsequently by diffuse pulmonary fibrosis. Although a low compliance is not universally included as a diagnostic criterion of ARDS, it is a constant feature of the syndrome and requires accurate evaluation to optimize mechanical ventilatory support:

Compliance of the respiratory system

$$= \frac{V_T}{Paw - \text{total PEEP}} \quad (1)$$

Compliance of the lung

$$= \frac{V_T}{(Paw - Poes) - \text{total PEEP}} \quad (2)$$

where *P*aw and *P*oes are the pressures measured during a 2-s end-inspiratory pause (plateau pressure) at the airway and oesophagus respectively; total PEEP is the sum of both applied and intrinsic positive end-expiratory pressure (auto-PEEP) [46]. The determination of respiratory compliance in patients with ARDS should include:

(a) measurement of plateau pressure at several lung volumes;
(b) measurement of auto-PEEP;
(c) when deemed necessary, measurement of intrathoracic pressure, to separately evaluate lung and chest wall compliance.

Methods currently employed to assess static respiratory compliance deliver small incremental volumes to a sedated and fully relaxed patient. A series of inflations are used to compute a pressure–volume curve, the slope determining the compliance of the respiratory system. To separate the lung and chest wall contributions, intrathoracic pressure is estimated with an oesophageal balloon. During ALI the compliance of the respiratory system is assumed to be primarily determined by lung compliance. Occasionally, chest wall compliance is reduced (e.g. abdominal distension, circumferential burns, tight bandages or massive oedema of the trunk) and measurement of oesophageal pressure is necessary to determine lung and chest wall compliance.

Significant increases of airway resistance are atypical of established ARDS, which is primarily viewed as a syndrome of reduced compliance. However, an increased resistive component [27] should be sought in the early phases of ALI, when bronchial inflammation is apparent and bronchoconstrictor mediators may be released.

Prognosis

When ALI progresses to established ARDS, a mortality rate near 60% has been reported consistently [1, 2, 8, 43, 52, 62]. The patient's prognosis is worsened by risk factors such as advanced age, pre-existing diseases and sepsis, regardless of whether the latter is the cause or a complication of

Table 4 Incidence and mortality rate of the acute respiratory distress syndrome (ARDS) in three studies: the NIH collaborative study of extracorporeal support [62], the European collaborative study of ARDS [1] and the Multicenter Registry of patients with ARDS [52]. (* Since the diagnosis of sepsis includes patients with infectious pneumonia, the total incidence of the individual aetiological factors is greater than 100%)

	Incidence (%)			Mortality (%)		
Aetiology	NIH	EUR	MR	NIH	EUR	MR
Number of patients	741	583	153			
Year	1979	1987	1992			
Aspiration pneumonitis	12	11	12	67	60	NA
Infectious pneumonia	25	30	31	69	61	NA
Trauma	7	19	35	47	38	42
Sepsis*	38	55	63	69	68	64
Total mortality (%)				66	59	54

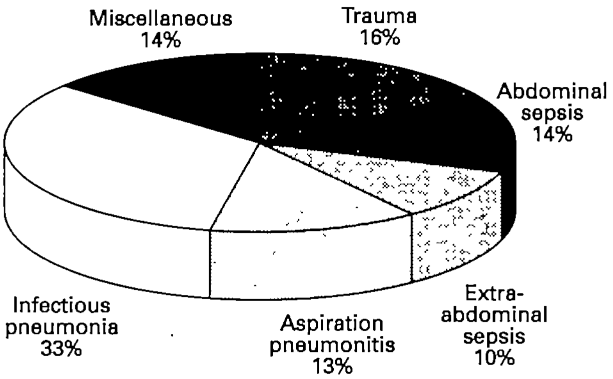

Figure 2 Aetiology of acute lung injury/acute respiratory distress syndrome in the European collaborative study of ARDS. (Modified with permission from Artigas and colleagues [1].)

ARDS. The combination of two or more such risk factors (e.g. age over 60 and sepsis) with ALI can raise the mortality rate to 70–90%. Table 4 summarizes the incidence and prognosis of the most frequent aetiologies of ALI, as reported in three large clinical studies over the past two decades: the NIH collaborative study of extracorporeal support [62], the European collaborative study of ARDS [1] and the Multicenter Registry of patients with ARDS [52]. Even though the entry criteria of the most recent of these studies [52], are rather liberal and approach the current definition of ALI [4], the frequency and mortality rates of each aetiological category of ARDS were comparable in all three studies. Figure 2 illustrates the distribution of the most common aetiologies of ARDS in the European Collaborative Study [1]. Figure 3, obtained from the data of the Multicenter Registry of patients with ARDS [52], illustrates the direct correlation of mortality with increasing age, as well as with the number of aetiological factors causing ALI present at the time of diagnosis. The development of new organ system failures (e.g. liver failure, renal failure) during the evolution of ALI greatly increases the mortality rate, reaching 80–90% when more than three organ systems fail [1].

An increasing survival rate of patients with ARDS has recently been suggested, using temporal survival trend analysis [41, 43]. While the survival rate of high risk patients (i.e. those with advanced age or multiple risk factors) is essentially unchanged from earlier periods, younger patients, after traumatic injury and without overt infection, appear to have a significantly better chance of survival when compared with 10 or 20 years ago. This may be a reflection of an overall improvement of intensive care therapies for all critically ill patients, improved ventilatory and pharmacological support, or all three. Not all studies, however, report enhanced survival rates [52] and careful, prospective data collection is needed.

For the survivors of ARDS, lung function often recovers significantly, allowing the survivors of this devastating syndrome to lead a productive life. The degree of residual impairment of respiratory function correlates with the severity of ARDS [39]. After a prolonged hospital course, recovery of lung function (both subjective function and spirometry) continues for several months, and plateaus at 3–6 months. At this time, the total lung capacity, vital capacity and DL_{CO} reach approximately 70% of the predicted normal values [39].

Therapeutic approaches to ALI

There is widespread agreement on the basic therapeutic principles for treating ALI: admission to the ICU, treatment of the underlying condition, use of supplemental oxygen and mechanical ventilation with PEEP, avoidance of oxygen toxicity and of fluid overload. Beyond this, practices vary widely. We will discuss both common and novel therapies.

PREVENTION AND TREATMENT OF THE UNDERLYING CONDITION

Limiting the incidence and severity of the various aetiologies known to cause ALI is the most sensible way of preventing ARDS. Since ARDS is a relatively uncommon occurrence (5 to 25 cases per 100000 individuals per year) [34, 55] any prospective evaluation of preventive measures requires a large number of subjects. One way to overcome this problem in planning studies of ARDS is to select a patient population known to be at high risk of developing the syndrome [11]. Another approach is to liberalize the definition of ARDS and thereby increase its rate of diagnosis. This strategy was promoted at the American-European Consensus Conference on ARDS [4] and prompted the introduction of the term ALI to include earlier and less severe forms of ARDS.

General principles of sound clinical practice are important for the prevention of ALI: early drainage of abscesses, debridement of devitalized tissue, rapid fixation of fractures, grafting of burn scars, adequate volume resuscitation of hypovolaemic states, appropriate use of antibiotics and sterile techniques, etc. Certain additional interventions aimed at limiting the incidence or severity of ALI have been proposed.

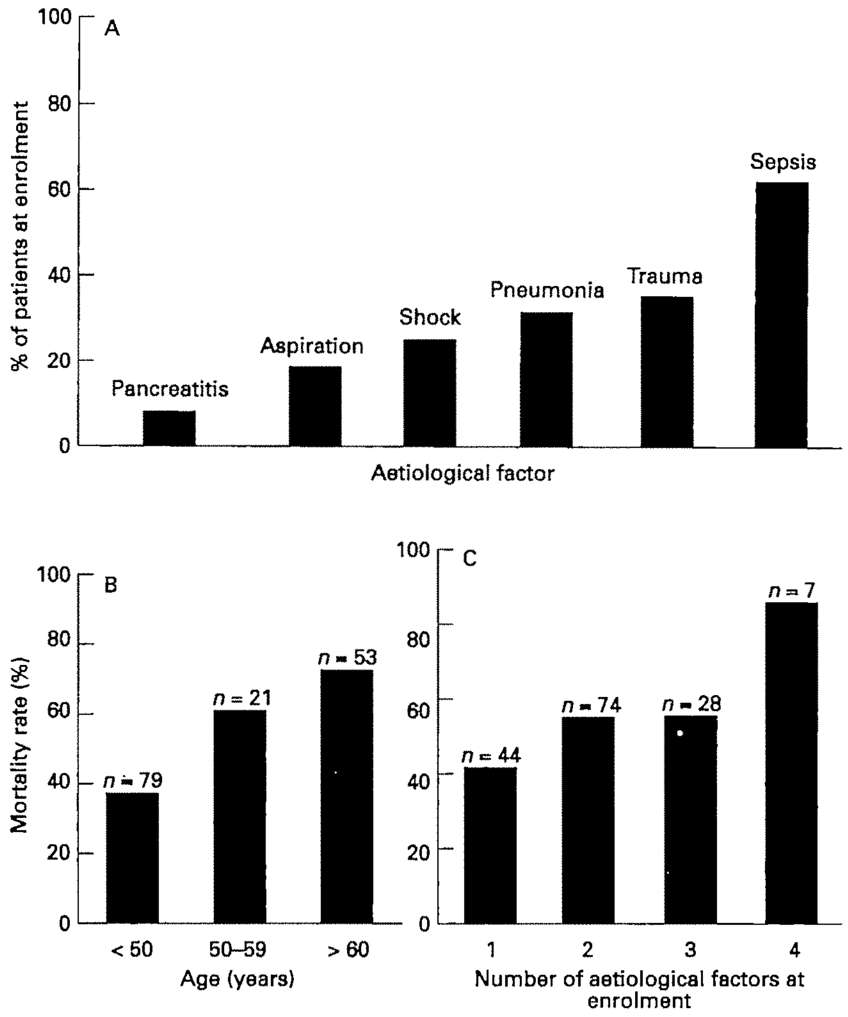

Figure 3 Predictors of mortality rate in a prospectively studied population of 153 patients with acute lung injury/acute respiratory distress syndrome. Modified with permission from Sloane and colleagues [52]. A: shows the incidence of some of the most common aetiological factors; more than one aetiological factor was often recorded. B: shows the effect of increasing age on the mortality rate. C: shows the effect on the mortality rate of the combination of multiple aetiological factors at the time of enrolment.

"Supranormal" haemodynamic management

The practice of "supranormal" [51] haemodynamic resuscitation with i.v. fluids and pressors has been proposed to improve the therapy of critically ill patients, including those with ARDS [10, 13]. A hidden tissue oxygen debt, unmasked by "supranormal" resuscitation, was suggested to negatively affect the prognosis of ARDS and several other critical illnesses. Despite enthusiasm for this approach in the treatment of trauma victims and septic patients, its effect is controversial [50]. Two large recent trials [24, 29] of critically ill patients, including ARDS patients, showed no benefit of "supranormal" resuscitation on the overall survival rate or the evolution of respiratory failure.

Prophylaxis of chemical and bacterial aspiration

Aspiration of gastric contents is a frequent aetiology of ALI. Prophylaxis includes watchful assessment of the patients' ability to protect the airway, skilful airway management at the time of and after tracheal intubation, and possibly (controlled data are not available) stimulation of gut motility with cholinergic agents such as metoclopramide. In addition, pharmacological interventions have been examined to learn if they reduce the incidence of nosocomial pneumonia and consequent ARDS through decontamination of the gastrointestinal tract. Oral or gastric administration of sucralphate (a sucrose sulphate and aluminium hydroxide salt) for stress ulcer prophylaxis prevents Gram-negative bacillary overgrowth of the proximal gastrointestinal tract of intubated patients and may decrease the incidence of nosocomial pneumonia in comparison with therapy with antacids and histamine receptor antagonist [18]. Selective gastrointestinal decontamination with non-absorbable antibiotics has also been proposed to prevent aspiration of bacteria into the tracheobronchial tree. However, clinical trials failed to show a decreased incidence of nosocomial pneumonia following selective decontamination [22].

Prophylaxis of transfusion-related ALI (TRALI)

TRALI may occur when human leucocyte antibodies (HLA) are transfused via a plasma-containing blood product, i.e. fresh frozen plasma, whole blood or packed red blood cells [20]. The combination of these antibodies with the host's marginated pool of granulocytes (the majority of which reside in the lung) activates the complement pathway generating an inflammatory reaction leading to ALI. Characterization of the pathogenesis of TRALI is recent. What was previously considered to be a risk factor for ARDS, massive blood transfusions, is probably TRALI. The incidence of TRALI is unknown since patients who develop ALI after blood transfusions often have other risk factors capable of producing lung injury and it is often difficult to isolate a single responsible aetiology. A laboratory diagnosis of TRALI is supported by HLA antibody screening of the donor blood. Prevention of TRALI [20] may be possible through donor selection and pre-testing: multiparous women and previously transfused subjects are most likely to donate HLA antibodies.

Anti-inflammatory therapy: corticosteroids

Several clinical trials of corticosteroid therapy for the treatment of early sepsis and the treatment or prevention of ARDS were conducted in the past decade [5, 11]. A sub-study of a large sepsis trial [11] prospectively evaluated the effects of 24 h of treatment with methylprednisolone, 30 mg kg^{-1} i.v. every 6 h, on the development of ARDS in patients with the sepsis syndrome. They found no beneficial effect; in fact, greater mortality occurred in the treated group. Another large study [5] failed to detect any benefits of a similar methylprednisolone regimen for the treatment of established ARDS. Despite these negative results, corticosteroid therapy has been proposed for the treatment of the late fibroproliferative phase of ARDS [40]. There are no controlled data to support this approach. On the other hand, there are risks, chiefly an increased susceptibility to infection [11, 40].

Anti-inflammatory therapy: immunological agents

New pharmacological agents aimed at blocking the mediators of the inflammatory response have been tested in the laboratory and clinical trials. Various monoclonal antibodies directed against endotoxin or cytokines, as well as naturally occurring antagonists of cytokine receptors, have been studied. A clear synopsis of the status of this complex field has been published [3]. Most of the clinical trials thus far completed were directed at treating the large group of patients with the sepsis syndrome and provided few data regarding their effects upon respiratory parameters. In one study, a prospectively defined analysis of a subgroup of patients with ARDS was included [8] and reported no effect of a human anti-endotoxin monoclonal antibody on the survival or resolution of ARDS. The results of most clinical trials of immunotherapy have thus far been disappointing [3] and no agent aimed at blocking the immunological response of septic critically ill patients is available. A broader and less selective approach to immunotherapy employs the use of anti-inflammatory agents that have well known pharmacological and safety profiles. One of these agents, the cyclo-oxygenase inhibitor ibuprofen, has produced encouraging results in a phase II trial of septic patients [6]. A large, multicentre trial of i.v. ibuprofen (10 mg kg^{-1} every 6 h for 48 h) in patients with the sepsis syndrome and related ARDS has recently been completed [3].

SUPPORTIVE THERAPY

Significant progress has taken place in the past 10 years in the area of supportive therapy for acute respiratory failure. Although these advances have not been clearly shown to improve the overall survival rate of patients with severe ARDS, we believe they have contributed to our ability to care for these patients and our knowledge of the syndrome.

A novel approach to mechanical ventilation

The traditional manner of ventilating patients with ALI delivers large tidal volumes (10 to 15 ml kg^{-1}), minimizes inspired oxygen fraction ($F_{I_{O_2}}$) and maintains normal arterial oxygen and carbon dioxide tensions. Significant changes of this practice have been proposed based upon increased understanding of the traumatic effects of mechanical ventilation on the lung [37, 53]. Lung tissue damage from mechanical ventilation was demonstrated early after the widespread introduction of positive pressure ventilation for acute respiratory failure [45], but the implication of these early data became clearer 20 years later, when studies from Europe [15] and the USA [56] provided unequivocal evidence of severe lung damage produced in normal animals by large inflation volumes (*volotrauma*). A further line of research underscored the importance of volotrauma by demonstrating that during early ALI the recruitable lung volume is significantly reduced. By imaging the lungs of early ARDS patients with high resolution computed tomography (CT), the parenchyma revealed surprisingly inhomogeneous lesions [26, 38], with areas of consolidation in dependent lung regions and areas of normal radiographic density in non-dependent regions (fig. 4). By combining traditional physiological analysis with CT imaging, Gattinoni and colleagues [26] reported that the mechanical properties of the lung were similarly inhomogeneously distributed: areas of consolidation had a significantly reduced compliance whereas lung regions that appeared normally aerated had a normal compliance. Thus, a tidal volume of 10–15 ml kg^{-1} may be excessive when the portion of lung parenchyma susceptible to recruitment is only 30 % of the total lung mass.

While the main determinant of volotrauma is the lung volume at end inspiration [16], this cannot be routinely measured, and airway pressure is commonly employed to estimate the degree of distension associated with tidal ventilation. Lung tissue trauma may occur if the lung is underinflated and alveoli collapse at end expiration: it is also believed that cyclic alveolar opening and closing during tidal breathing may induce tissue and surfactant damage [44]. It seems ideal, therefore, to attempt to individually determine the appropriate lung volume at which each patient with ALI should be mechanically ventilated to produce the least volotrauma. The ideal

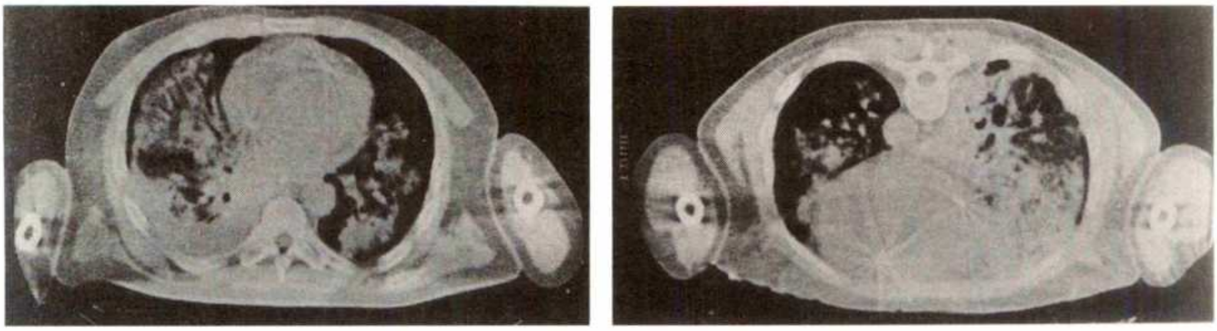

Figure 4 High resolution computed tomogram of a patient with early acute respiratory distress syndrome. Left: supine. Right: prone. Note the inhomogeneous lung opacities, preferentially distributed along a gravitational gradient. (Reproduced with permission from Gattinoni and colleagues [25].)

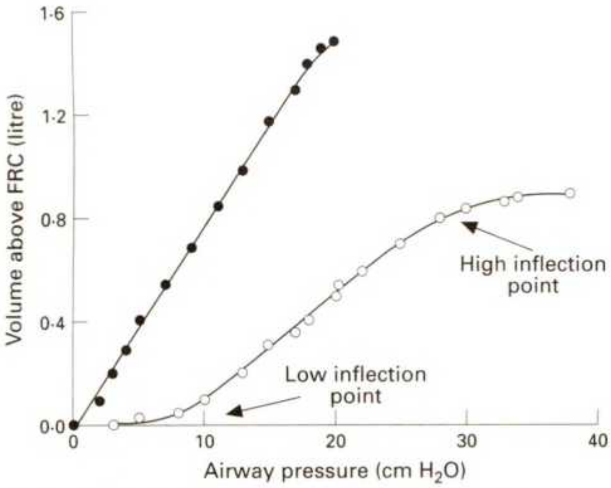

Figure 5 Idealized static pressure–volume curves of the respiratory system of a subject with normal respiratory mechanics (left, compliance = 80 ml cm H_2O^{-1}) and of a patient with acute respiratory distress syndrome (ARDS, right, compliance = 30 ml cm H_2O^{-1}). The ARDS curve presents two inflection points, the lower occurring at approximately 8 cm H_2O (suggested level to set PEEP) and the higher occurring at approximately 28 cm H_2O (suggested maximum end-inspiratory plateau pressure). (●) Normal, (○) ARDS.

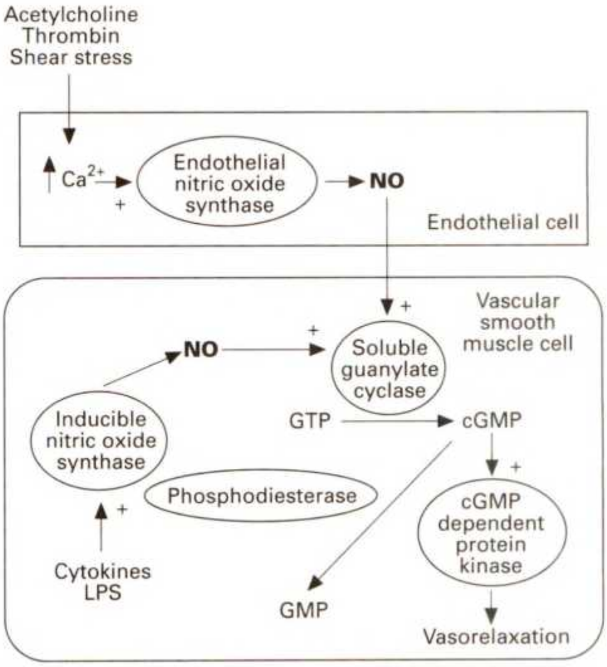
Acetylcholine
Thrombin
Shear stress
Ca^{2+}
+
Endothelial nitric oxide synthase
NO
Endothelial cell
+
Vascular smooth muscle cell
NO
+
Soluble guanylate cyclase
Inducible nitric oxide synthase
GTP
cGMP
+
Phosphodiesterase
+
cGMP dependent protein kinase
Cytokines
LPS
GMP
Vasorelaxation

Figure 6 Nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway in the vascular wall. (Reproduced with permission from Ichinose and colleagues [32].)

ventilatory pattern may be determined by constructing a pressure–volume curve of the respiratory system (or the lung when indicated) as previously described. A number of studies [17, 19, 26, 44, 49] indicate that the static pressure–volume curve of the respiratory system during ARDS is sigmoid-shaped, with both lower and higher "inflection points" denoting the range of pressure and volume at which the tidal ventilation should be delivered to minimize volotrauma: a PEEP level of 10–15 cm H_2O and an end-inspiratory plateau pressure of 30 to 35 cm H_2O are sufficient in most circumstances to avoid both alveolar collapse and overstretching. Roupie and colleagues [49] obtained static pressure–volume curves in patients with and without ARDS. They demonstrated that in patients with mild respiratory failure the curves were steep and linear, not differing from normal compliance curves of the respiratory system. In contrast, for patients with ARDS the pressure–volume curve was shifted to the right and in most cases displayed both low and high "inflection points" occurring at approximately 10 and 30 cm H_2O inspiratory plateau pressure, respectively. Figure 5 shows an idealized pressure–volume curve of the lung during ARDS, with a reduced slope and two inflection points, and it clearly contrasts with a normal compliance curve.

At times, limiting the peak inflation pressure (and thus the end-inspiratory volume) below the high inflection point of the pressure–volume curve may only be accomplished by markedly reducing the tidal volume (e.g. $\leqslant 6$ ml kg^{-1}) in which case hypercarbia ensues at normal respiratory rates. The growing clinical practice of allowing the arterial carbon dioxide tension to rise gradually, providing enough time for renal compensation of the respiratory acidosis by retaining anions, has been given the term *permissive hypercapnia* [19]. Despite widespread enthusiasm, there is presently no evidence that this style of ventilatory management improves the outcome of patients with ALI.

INHALED NITRIC OXIDE

Nitric oxide (NO) is a potent endogenous vasodilator, produced in endothelial cells by cleavage of the amino-acid L-arginine by the various isoforms of

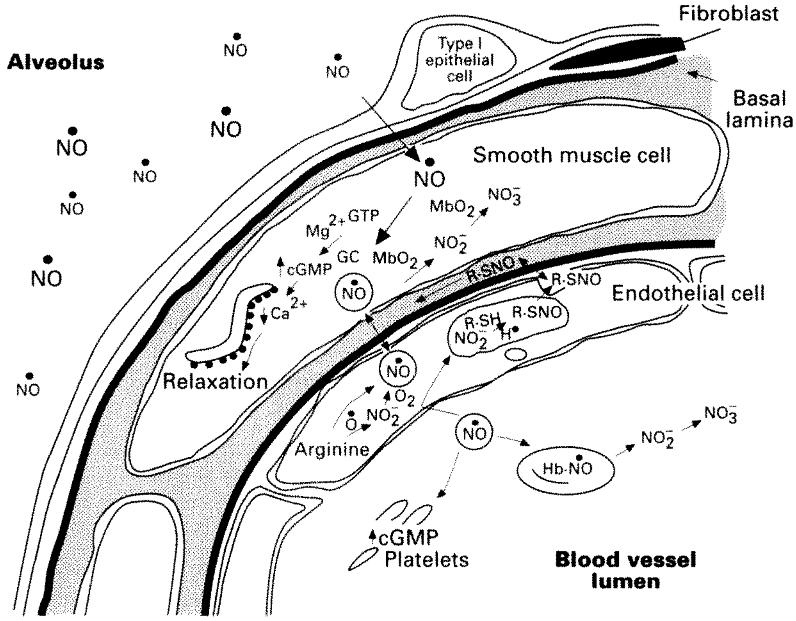

Figure 7 Effects of inhaled nitric oxide (NO) on acute pulmonary hypertension associated with acute respiratory failure. (Reproduced with permission from Frattacci and colleagues [21].)

NO synthase [42]. Nitric oxide is an unstable free radical that accounts for the activity of endothelium-derived relaxing factor as well as for other important biologic activities [23, 42]. The vasodilator action of NO (fig. 6) is mediated through an increase of cGMP within the smooth muscle cells of the vascular wall. Other cGMP-mediated properties of NO include the modulation of neurotransmission, bronchodilatation and inhibition of platelet aggregation. When exogenous NO gas is inhaled (fig. 7) it produces profound local vasodilatation in ventilated regions of the lung and reverses the pulmonary vasoconstriction due to hypoxaemia (HPV) and other vasoconstrictor stimuli [60]. In tissues, NO rapidly degrades to nitrates and nitrites with little biological activity. When NO diffuses into the blood vessels, it combines rapidly with circulating haemoglobin and is inactivated. The resulting nitrosyl–haemoglobin is oxidized to methaemoglobin. These biological properties make NO an ideal agent to produce selective pulmonary vasodilatation without inducing systemic vasodilatation. Furthermore, producing selective vasodilatation of well ventilated areas of the pulmonary vasculature improves the matching of ventilation to perfusion [47]. Following the earliest clinical trials of NO inhalation in patients with ARDS [9, 48], a number of centres in the USA and Europe have administered NO under investigational protocols as part of the treatment of ALI. The current status of this innovative therapy can be summarized as follows.

In approximately 70 % of patients with established ARDS, when breathing NO the arterial oxygen tension increases and pulmonary hypertension decreases by at least 20 % of baseline [36]. This response is sufficient to allow a decreased level of ventilatory support, reducing either the $F\text{I}_{O_2}$ or PEEP level. ARDS patients most likely to respond favourably are those with a high pulmonary vascular resistance [9, 36]. Very low inhaled NO concentrations are sufficient to elicit a significant increase of the Pa_{O_2}: 5 to 20 parts per million (ppm) [9, 48]. Toxicity is minor or unmeasurable at low inspired NO concentrations [23]. The effect of NO treatment on outcome is unknown; results from large randomized trials of NO inhalation in ARDS patients in Europe and North America will be available in several years.

EXTRACORPOREAL TECHNIQUES OF GAS EXCHANGE

Extracorporeal membrane oxygenation (ECMO) for acute respiratory failure was introduced to clinical practice about 25 years ago. The concept behind the use of ECMO in patients with acute respiratory failure is to provide a temporary "substitute" for transpulmonary respiration while the severely injured lungs are allowed to recover. After initial, anecdotal reports of positive results, a multicentre trial sponsored by the National Institutes of Health (NIH) failed to show any advantage of veno–arterial ECMO over traditional mechanical ventilation in severe ARDS [62]. In the ensuing years, technical progress has made the practice of ECMO safer and less cumbersome, and several centres throughout the world have acquired great skill, reporting excellent results. A second NIH-sponsored trial was designed to test the effect of a newer mode of extracorporeal gas exchange, extracorporeal carbon dioxide removal provided via veno–venous perfusion. Unfortunately, this trial also failed to show any significant benefit over traditional mechanical ventilation [43]. The practice of extracorporeal gas exchange in adults remains limited to a few, highly specialized centres in the USA and Europe.

Surfactant

Replacement therapy with lung surfactant has been pursued for the treatment of ALI, particularly when aspiration pneumonitis is the suspected aetiology.

Both natural and synthetic preparations are being studied. There is evidence that pulmonary surfactant is dysfunctional in animal models of aspiration pneumonitis as well as in adults with ALI [28]. Despite highly successful use of surfactant therapy in newborns with the respiratory distress syndrome and evidence for favourable physiological responses in animal models, as well as preliminary clinical observations [57], there are no clinical trials to support the use of surfactant in adults with ALI.

OTHER EXPERIMENTAL TECHNIQUES

The *intravenous oxygenator* (IVOX) is a device composed of a bundle of hollow polypropylene fibres, inserted percutaneously into the inferior vena cava, where venous blood flows over the hollow fibres and oxygen and carbon dioxide are exchanged. Only preliminary data from the FDA phase II trial are available. With the present technology the IVOX does not seem to make a significant impact upon gas exchange in severe ARDS [30].

Partial *liquid ventilation* requires ventilation of the lungs with perfluorocarbon. The high density and low surface tension of perfluorocarbon enhances the recruitment of dependent lung regions, improves ventilation to perfusion matching and favours the removal of airways secretions. Only very preliminary data regarding safety and suitability of this technique in ARDS are available [31]. More encouraging data have been reported in a small number of infants and children with severe acute respiratory failure treated with perfluorocarbon [31].

Conclusions

Acute lung injury of multiple aetiologies may lead to a severe form of acute respiratory failure, the acute respiratory distress syndrome (ARDS). The mortality rate of ARDS is very high, despite the scientific and technological advances in the care of critically ill patients of the past 30 years. Recent data, however, suggest that the prognosis of ARDS has improved in selected populations, particularly younger patients without overwhelming infection. These observations, together with our growing knowledge of the pathophysiology of acute respiratory failure, should encourage investigators and clinicians to continue their efforts to better understand and treat acute lung injury. Future directions of research and clinical activity in this field include:

(a) Early intervention. Treatment of the underlying aetiology, maintenance of adequate organ perfusion and appropriate ventilatory management may reduce the incidence of infection and of iatrogenic complications and thereby increase survival. New experimental approaches such as nitric oxide inhalation and permissive hypercapnia should be targeted at the earliest stages of acute respiratory failure.

(b) Researching the earliest humoral and cellular mechanisms producing the initial acute injury may provide clinicians with future therapies to apply early in the course of acute respiratory failure.

(c) Clinical trials of novel and promising therapies should be designed by experienced clinical investigators. Trials should include adequate numbers of patients with ARDS of similar aetiology, include multiple institutions and, ideally, they should be sponsored by an impartial agency. The next few years will be exciting ones for those clinicians and investigators who are interested in the treatment of ALI and ARDS, because the results of several clinical trials will become available. The ibuprofen study should soon be published. Two large clinical trials of inhaled nitric oxide are under way. A 7-year, multicentre programme has been funded by the NIH to implement large scale clinical trials of novel treatments for ARDS. The first of such studies will compare traditional, large-tidal volume ventilation with reduced tidal volumes and airway pressures.

References

1. Artigas A, Le Gall JR, Carlet J, Blanch L, Fernandez R. Clinical presentation, prognostic factors, and outcome of ARDS in the European collaborative study (1985–1987). In: Zapol WM, Lemaire F, eds. *Adult Respiratory Distress Syndrome*. New York: Marcel Dekker, 1991: 37–63.
2. Ashbaugh DG, Bigelow DB, Petty TL. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–323.
3. Bernard G. Sepsis trials. Intersection of investigation, regulation, funding and practice. *American Journal of Respiratory and Critical Care Medicine* 1995; **152**: 4–10.
4. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R and the Consensus Committee. The American-European Consensus Conference of ARDS. Definitions, mechanisms, relevant outcomes and clinical trial coordination. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 818–824.
5. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz GA, Harris TR, Brigham KL. High dose corticosteroids in patients with the adult respiratory distress syndrome. *New England Journal of Medicine* 1987; **317**: 1565–1570.
6. Bernard GE, Reines HD, Halushka PV, Higgins SB, Metz CA, Swindell BB, Wright PE, Watts FL, Vrbanac JJ. Prostacyclin and thromboxane A_2 formation is increased in human sepsis syndrome. Effect of cyclooxygenase inhibition. *American Review of Respiratory Diseases* 1991; **144**: 1095–1101.
7. Bertozzi P, Astedt B, Zenzius L, Lynch K, LeMaire F, Zapol WM, Chapman HA. Depressed broncho-alveolar urokinase activity in patients with adult respiratory distress syndrome. *New England Journal of Medicine* 1990; **322**: 890–897.
8. Bigatello L, Greene RE, Sprung CL, Panaceck EA, Straube RC, Zimmerman JL, Maunder RJ, Lanken PN, Stanek KS, Zaslavsky A, Zapol WM. HA-1A in septic patients with ARDS: results from the pivotal trial. *Intensive Care Medicine* 1994; **20**: 328–334.
9. Bigatello LM, Hurford WE, Kacmarek RE, Roberts JD, jr, Zapol WM. Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. Effects on pulmonary hemodynamics and oxygenation. *Anesthesiology* 1994; **80**: 761–770.
10. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *New England Journal of Medicine* 1987; **317**: 397–403.
11. Bone RC, Fisher C, Clemmer TP, Slotman GJ, Metz CA, and the Methylprednisolone Severe Sepsis Study Group. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. *Chest* 1987; **92**: 1032–1036.
12. Brigham KL, Meyrick B. Endotoxin and lung injury. *American Review of Respiratory Diseases* 1986; **133**: 913–927.
13. Danek SJ, Lynch JP, Weg JG, Dantzker DR. The dependence of oxygen uptake on oxygen delivery in the adult

respiratory distress syndrome. *American Review of Respiratory Diseases* 1980; **122**: 387–395.

14. Deby-Dupont G, Lamy M, Faymonville ME, Adam A, Damas P, Deby C, Franchimont P. Proteases and antiproteases in the adult respiratory distress syndrome. In: Zapol WM, Lemaire F, eds. *Adult Respiratory Distress Syndrome*. New York, Marcel Dekker, 1991: 305–352.
15. Dreyfuss D, Basset P, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *American Review of Respiratory Diseases* 1985; **132**: 880–884.
16. Dreyfuss D, Saumon G. The role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine* 1993; **148**: 1194–1203.
17. Dreyfuss D, Soler P, Saumon G. Mechanical ventilation-induced pulmonary edema. Interactions with previous lung alterations. *American Journal of Respiratory and Critical Care Medicine* 1995; **151**: 1568–1575.
18. Driks MR, Craven DE, Celli BR, Manning M, Burke RE, Garvin GM, Kunches LM, Farber HW, Wedel SA, McCabe WR. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. *New England Journal of Medicine* 1987; **317**: 1376–1382.
19. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 1722–1737.
20. Florell SR, Velasco SE, Fine PG. Perioperative recognition, management and pathologic diagnosis of transfusion-related acute lung injury. *Anesthesiology* 1994; **81**: 508–510.
21. Frattacci M-D, Frostell CG, Chen T-Y, Wain JC, Robinson DR, Zapol WM. Inhaled nitric oxide. A selective pulmonary vasodilator of heparin-protamine vasoconstriction in sheep. *Anesthesiology* 1991; **75**: 990–999.
22. Gastinne H, Wolff M, Delatour F, Faurisson F, Chevret S for the French study group on selective decontamination of the digestive tract. A controlled trial in intensive care units of selective decontamination of the digestive tract with non absorbable antibiotics. *New England Journal of Medicine* 1992; **326**: 594–599.
23. Gaston B, Drazen J, Loscalzo J, Stamler J. The biology of nitrogen dioxides in the airways. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 538–551.
24. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R and the S_vO_2 Collaborative Group. A trial of goal-oriented hemodynamic therapy in critically ill patients. *New England Journal of Medicine* 1995; **333**: 1025–1032.
25. Gattinoni L, Pelosi P, Vitale G, Pesenti C, D'Andrea L, Mascheroni D. Body position changes redistribute tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991, **74**: 15–23.
26. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of the total respiratory system in acute respiratory failure. *American Review of Respiratory Diseases* 1987; **136**: 730–738.
27. Gottfried SB, Rossi A, Higgs BD, Calverley PMA, Zocchi L, Bozic C, Milic-Emili J. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. *American Review of Respiratory Diseases* 1985; **131**: 414–420.
28. Gregory TJ, Longmore WJ, Moxley MA, Whitsett JA, Reed CR, Fowler AA, Hudson LD, Crim C, Hyers TM. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *Journal of Clinical Investigation* 1991; **88**: 1976–1981.
29. Hayes M, Timmins AC, Yau EHS, Palazzo M, Hinds C, Watson D. Elevation of systemic oxygen delivery in critically ill patients. *New England Journal of Medicine* 1994; **330**: 1717–1722.
30. High KM, Snider MT, Richard R, Russell GB, Stene JK, Campbell DB, Aufiero TX, Thieme GA. Clinical trials of an intravenous oxygenator in patients with adult respiratory distress syndrome. *Anesthesiology* 1992; **77**: 856–863.
31. Hirschl RB, Pranikoff T, Gauger P, Schreiner RJ, Dechert R, Bartlett RH. Liquid ventilation in adults, children and full-term neonates. *Lancet* 1995; **346**: 1201–1202.
32. Ichinose F, Hurford W, Zapol WM. Evaluation of inhaled nitric oxide in experimental models of lung injury. In: Zapol WM, Bloch K, eds. *Nitric Oxide and the Lung*. New York: Marcel Dekker (in press).
33. Katzenstein A, Asken FB. Acute lung injury patterns: diffuse alveolar damage, acute interstitial pneumonia, bronchiolitis obliterans-organizing pneumonia. In: *Surgical Pathology of the Non-Neoplastic Lung Diseases*. 2nd ed. Philadelphia: WB Saunders, 1990: 9–57.
34. Lewandowski K, Metz J, Deutschmann C, Prieb H, Khulen R, Artigas A, Falke K. Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. *American Journal of Respiratory and Critical Care Medicine* 1995; **151**: 1121–1125.
35. Loscalzo JL. Nitric oxide and vascular disease. [Editorial.] *New England Journal of Medicine* 1995; **333**: 251–252.
36. Manktelow C, Bigatello LM, Hess D, Hurford WE. Evaluation of the initial response to inhaled nitric oxide (NO) in patients with ARDS. [*Abstract*, submitted to the International Conference of the American Thoracic Society, New Orleans, LA, May 1996.]
37. Marini JJ, Kelsen SG. Re-targeting ventilatory objectives in the adult respiratory distress syndrome. New treatment prospects-persistent questions. *American Review of Respiratory Diseases* 1992; **146**: 2–3.
38. Maunder RJ, Shuman WP, McHugh JW, Marglin SI, Butler J. Preservation of normal lung region in the adult respiratory distress syndrome. Analysis by computed tomography. *Journal of the American Medical Association* 1986; **255**: 2463–2465.
39. McHugh LG, Milberg JA, Whitcomb ME, Schoene RB, Maunder RJ, Hudson L. Recovery of function in survivors of the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 90–94.
40. Meduri GU, Belenchia JM, Estes RJ, Wundernik RG, El Torky M, Leeper KV. Fibroproliferative phase of ARDS. Clinical findings and effects of corticosteroids. *Chest* 1991; **100**: 943–952.
41. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. *Journal of the American Medical Association* 1995; **273**: 306–309.
42. Moncada S, Higgins A. Mechanisms of disease: the L-arginine-nitric oxide pathway. *New England Journal of Medicine* 1993; **329**: 2002–2012.
43. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Weaver LK, Dean NC, Thomas F, East TD, Pace NL, Suchyta MR, Beck E, Bombino M, Sittig DF, Bohm S, Hoffman B, Becks H, Butler S, Pearl J, Rasmusson B. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 295–305.
44. Muscedere JG, Mullen JBM, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 1327–1334.
45. Opie LH, Spaulding JMK, Stoff AF. Mechanical properties of the chest during intermittent positive pressure respiration. *Lancet* 1959; **1**: 545–550.
46. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. *American Review of Respiratory Diseases* 1982; **126**: 166–170.
47. Pison U, Lopez FA, Heildelmeier CF, Rossaint R, Falke KJ. Inhaled nitric oxide reverses hypoxic pulmonary vasoconstriction without impairing gas exchange. *Journal of Applied Physiology* 1993; **74**: 1287–1292.
48. Rossaint R, Falke KJ, Lopez F, Slama K, Pison W, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328**: 399–405.
49. Rupie E, Dambrosio M, Servillo G, Mentec H, El Atrous, Beydon L, Brun-Buisson C, Lemaire F, Brochard L. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine* 1995; **152**: 121–128.
50. Russell JA, Phang PT. The oxygen delivery/consumption controversy. Approaches to management of the critically ill. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 533–537.
51. Shoemaker WC, Appel P, Bland R. Use of physiologic

monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. *American Journal of Surgery* 1983; **146**: 43–48.

52. Sloane PJ, Gee MH, Gottlieb JE, Albertine KH, Peters SP, Burns RJ, Machiedo G, Fish JE. A multicenter registry of patients with acute respiratory distress syndrome. Physiology and outcome. *American Review of Respiratory Diseases* 1987; **136**: 471–474.
53. Slutsky A, chairman. ACCP Consensus Conference. Mechanical ventilation. *Chest* 1993; **104**: 1833–1859.
54. Stewart TE, Valenza F, Ribeiro SP, Wener AD, Volgyesi G, Mullen BM, Slutsky AS. Increased nitric oxide in exhaled gas as an early marker of lung inflammation in a model of sepsis. *American Journal of Respiratory and Critical Care Medicine* 1995; **151**: 713–718.
55. Thomsen GE, Morris AH. Incidence of the adult respiratory distress syndrome in the state of Utah. *American Journal of Respiratory and Critical Care Medicine* 1995; **152**: 965–971.
56. Tsuno K, Prato P, Kolobow T. Acute lung injury from mechanical ventilation at moderately high airway pressures. *Journal of Applied Physiology* 1990; **69**: 956–961.
57. Weg JG, Balk RA, Tharratt RS, Jenkinson SG, Shah JB, Zaccardelli D, Horton J, Pettishall EN, for the Exosurf ARDS Sepsis Study Group. *Journal of the American Medical Association* 1994; **272**: 1433–1438.
58. Zapol WM, Jones R. Vascular components of ARDS: clinical pulmonary hemodynamics and morphology. *American Review of Respiratory Diseases* 1987; **136**: 471–474.
59. Zapol WM, Quist J, Tresland RL, Lemaire F. Pathophysiologic pathways of the adult respiratory distress syndrome. In: Tinker J, Zapol WM, eds. *Care of the Critically Ill Patient*, 2nd ed. London: Springer-Verlag, 1992; 435–455.
60. Zapol WM, Rimar S, Gillis N, Marletta M, Bosken C. Nitric oxide and the lung. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: 1375–1380.
61. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. *New England Journal of Medicine* 1977; **296**: 476–480.
62. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Pierce ECC, Thomas AN, Proctor HG, Drinker PA, Pratt PC, Bagniewski A, Miller RG. Extracorporeal membrane oxygenation in severe acute respiratory failure. *Journal of the American Medical Association* 1979; **242**: 2193–2196.

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Sepsis and cytokines: current status

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Sepsis syndrome represents a spectrum of pathophysiology that results from an exuberant host inflammatory response to a specific inciting event. The clinical course of sepsis syndrome ranges from mild physiological derangements to severe multiple organ dysfunction and death. In the United States, the incidence of sepsis syndrome has been estimated at 400000 cases annually, with a fatality rate of nearly 40%. The development of sepsis syndrome is related to a complex interplay of lipid, protein and possibly carbohydrate mediators. Although a large variety of mediators have been implicated in the development of sepsis syndrome, a rapidly growing body of experimental evidence suggests that proteins belonging to the cytokine family are decisive factors in determining the pathobiology of sepsis syndrome. This article reviews recent information which demonstrates the role of cytokines in the development of sepsis syndrome. Since cytokines play critical roles in the initiation and perpetuation of sepsis syndrome, we also review interventions which abrogate the actions of cytokines and might be effective treatments for sepsis syndrome and related disorders.

Sepsis syndrome

A consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine in 1991 proposed standardized terminology to define various aspects of sepsis syndrome [2]. These definitions stress the concept that the development of sepsis syndrome is related to a systemic inflammatory host response to an inciting event. The Consensus Conference recommended systemic inflammatory response syndrome (SIRS) as an umbrella term. SIRS is recognized by a constellation of cardinal signs which include tachypnoea, fever or hypothermia, tachycardia and leucocytosis or leucopenia with a "left shifted" differential white blood cell count. SIRS can result from either infectious or non-infectious conditions. Non-infectious conditions which are associated with SIRS include trauma, burns, haemorrhagic or hypovolaemic shock and pancreatitis. Sepsis is defined as SIRS which results from infection, which can be bacterial, paracystic, protozoan or viral. Although most cases of sepsis are related to Gram-negative infections, full blown sepsis can result from Gram-positive infections.

The severity of sepsis is proportional to the intensity of the host response. Severe sepsis is defined as sepsis which is associated with specific or multiple organ dysfunction. Septic shock occurs when there is systemic hypotension that is associated with tissue hypoperfusion and anaerobic metabolism. This simple classification system has been shown to predict mortality in a stepwise manner with a mortality of SIRS of 7%, sepsis of 16%, severe sepsis of 20% and septic shock of 46% [45]. This stratification of sepsis syndrome appears to reflect a continuum of systemic inflammation with increasing inflammation being associated with worsening clinical severity.

Cytokine hypothesis

Cytokines are a group of small signalling proteins produced by a large variety of cells that are thought to be important for host defence, wound healing and other essential host functions. Although cytokines are important for these homeostatic functions, excessive production and release of cytokines initiate widespread tissue injury which can result in organ dysfunction. Sepsis syndrome seems to result from overwhelming systemic inflammation which is caused by excessive release of cytokines into the systemic circulation.

The recent development of precise molecular tools for identifying and measuring cytokines has led to rapid accumulation of data implicating cytokines in the pathobiology of sepsis syndrome. Four cytokines, tumour necrosis factor α (TNFα), interleukin 1β (IL-1β), interleukin 6 (IL-6) and interleukin 8 (IL-8) have been most strongly associated with sepsis syndrome. In human and experimental animal models of sepsis, cytokines are released in a sequential manner resulting in a "cytokine cascade". The cytokine cascade is initiated when a stimulus such as Gram-negative bacterial endotoxin induces production and secretion of early or "proximal" cytokines, which include TNFα and IL-1β. TNFα

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Key words

Cells, metabolism. Protein, cytokines. Complications, infection. Infection, systemic inflammatory response syndrome.

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and IL-1β appear to mediate most of the physiological disturbances which are characteristic of sepsis. Infusion of either TNFα or IL-1β results in a sepsis-like state and specific blockers of either TNFα or IL-1β abrogate some of the manifestations of experimental sepsis. Proximal cytokines, as well as endotoxin, stimulate the production of later or "distal" cytokines, such as IL-6 and IL-8. Although the role of distal cytokines in sepsis is incompletely defined, they seem to intensify and perpetuate the inflammatory response and might have a role in tissue repair. IL-6 is a pleiotrophic mediator whose actions include modulation of lymphocyte function, activation of coagulation and induction of hepatic acute phase protein synthesis. Interestingly, IL-6 may down-regulate TNFα and IL-1β production, which might be important in limiting the inflammatory reaction. IL-8 is a potent activator and chemoattractant for polymorphonuclear leucocytes and is thought to mediate neutrophilic tissue inflammation. It is possible that IL-8 mediates neutrophilic inflammation in the lungs and other organs and that this process leads to tissue damage and organ dysfunction.

Cytokines are not stored in intracellular compartments and are newly synthesized and released in response to inflammatory stimuli. This regulation occurs predominantly at the level of gene transcription with new expression of cytokine mRNA. Specific transcription regulating proteins (transcription factors) regulate cytokine gene transcription by binding to regulatory portions of cytokine genes, and activating or inhibiting transcription. Each cytokine has a variety of transcription factor binding domains in the promoter region of its gene which interact in complex ways to control cytokine gene transcription.

Much progress has been made in recent years in understanding the actions of individual transcription factors and unravelling the interactions of these factors in regulating transcription of specific genes. One transcription factor, nuclear factor κB (NF-κB), appears to play a central role in regulating the cytokine cascade. NF-κB is activated in many cell types by stimuli such as endotoxin, TNFα and IL-1β. NF-κB activation and promoter binding are crucial for transcription of many cytokines and related molecules, including TNFα, IL-1β, IL-6 and IL-8 [55]. Further characterizing the roles of NF-κB and other transcription factors will probably lead to better understanding of the process that initiates and regulates the cytokine cascade. Since NF-κB may be a pivotal point of regulation for the cytokine cascade, interventions to inhibit NF-κB activation could down-regulate systemic inflammation to a much greater extent than blocking the production or action of a single cytokine.

In addition to activating a pro-inflammatory cytokine cascade, inflammatory stimuli activate the production of specific cytokine neutralizing molecules and counter-inflammatory cytokines that can modify the host inflammatory response. Cytokine neutralizing molecules include soluble cytokine receptors and cytokine receptor antagonists. Cytokine receptors have an extracellular binding domain, a hydrophobic membrane anchoring domain and an intracellular signal transducing domain. Soluble cytokine receptors result from proteolytic cleavage of the extracellular binding domain which can be released into the circulation. Soluble cytokine receptors have been identified for both the p75 and p55 TNF receptor, the IL-1 receptor and the IL-6 receptor. Cytokine receptor antagonists are cytokine-like molecules that bind to cell surface receptors but do not initiate signal transduction. A receptor antagonist has been identified only for IL-1 (IL-1ra).

Paradoxically, soluble TNF receptor (sTNFR) and IL-1ra are released into the circulation in 10–100-fold excess compared with TNFα and IL-1β. Naturally released cytokine antagonists modulate the *in vitro* biological actions of the corresponding cytokines, but their function and importance in human sepsis are not well understood. In patients with sepsis syndrome, prognosis may be determined, at least in part, by the balance of cytokines and cytokine neutralizing molecules. In patients with non-lethal sepsis, both IL-1ra and soluble cytokine receptors may be shed into the circulation in sufficient concentrations to neutralize the quantities of cytokines produced. However, the concentrations of these inhibitors may be inadequate to prevent the deleterious effects of exaggerated pro-inflammatory cytokine release which occurs in lethal septic shock.

Cytokines have synergistic, overlapping and antagonist effects. Counter-inflammatory cytokines as well as pro-inflammatory cytokines are produced following activation of the cytokine cascade. One counter-inflammatory cytokine, interleukin 10 (IL-10), is released into the circulation in human sepsis and has been shown to block the production of TNFα, IL-1β and IL-8 *in vitro*. IL-10, like IL-6, might have a role in limiting the systemic inflammatory reaction by regulating pro-inflammatory cytokine gene expression. The clinical manifestations of sepsis syndrome are probably determined by a complex interaction between pro-inflammatory cytokines, counter-inflammatory cytokines and cytokine neutralizing molecules.

Proximal cytokines

TUMOUR NECROSIS FACTOR α (TNFα)

TNFα is a primary mediator of inflammation, and has been implicated in a large number of infectious and non-infectious inflammatory diseases [58]. TNFα is a 17-kDa protein produced primarily by mononuclear phagocytes, which has pleiotrophic effects on target cells. Infusion of recombinant TNFα into humans results in SIRS with fever, haemodynamic abnormalities, leucopenia, elevated liver enzymes and coagulopathy [8, 51, 53, 64]. TNFα is capable of causing end-organ dysfunction which occurs in severe sepsis. In studies using chronically awake instrumented sheep, TNFa infusion caused pulmonary hypertension, hypoxaemia, decreased lung compliance and increases in pulmonary microvascular permeability [30, 71]. In human and animal models of sepsis induced by injection of bacterial endotoxin, TNFα production is quickly activated and can be detected in plasma.

Michie and colleagues infused *Escherichia coli* endotoxin into healthy volunteers and found that TNFα concentrations increased significantly and peaked 1 h after the infusion [39]. Several other studies have confirmed the observation that peak concentrations of TNFα are detected 60–90 min after endotoxin infusion [6, 28, 60].

TNFα appears to have a significant role in coordinating the inflammatory response and activating the cytokine cascade. *In vitro*, TNFα is a potent inducer of other cytokines, including IL + 1β, IL-6 and IL-8. In baboons injected with *E. coli*, treatment with TNFα antibodies decreased the production of IL-1β, IL-6 and IL-8, in addition to reducing morbidity and mortality [17, 21, 29, 46, 63].

TNFα can be detected in the plasma of many patients with sepsis, and concentrations generally correlate with severity of illness and outcome. Endo and colleagues [18] showed that TNFα, IL-1β, IL-6 and interleukin 2 (IL-2) concentrations in plasma were higher in patients with septic shock compared with patients with sepsis alone or with other causes of shock. Waage and colleagues [70] reported that 10 of 11 patients who died of meningococcaemia had elevated serum TNFα concentrations, while only eight of 68 survivors had similar elevations. In contrast with these findings, some studies have failed to show that initial TNFα concentrations predict outcome. For example, Casey, Balk and Bone [7] reported that concentrations of TNFα, IL-1β, IL-6 and endotoxin in patients with sepsis were elevated compared with patients in an intensive care unit without sepsis, but TNFα concentration did not predict mortality independently. In this study, only 54% of patients with sepsis had detectable plasma TNFα concentrations.

Other studies have suggested that persistently elevated plasma TNFα concentrations portend a poor prognosis in patients with sepsis. Martin and colleagues [36] evaluated plasma concentrations of TNFα and IL-6 serially in 30 patients with septic shock. All patients had elevated plasma TNFα and IL-6 concentrations. Non-survivors had persistently higher TNFα concentrations than survivors, but no differences were noted in IL-6 concentrations. Pinsky and colleagues [43] reported that TNFα and IL-6 concentrations were higher in septic than non-septic shock, and that persistence of IL-6 and TNFα in serum rather than peak concentrations predicted a poor outcome in patients with shock.

Since TNFα can be induced rapidly by endotoxin, causes a septic-like state after infusion, can activate production of other mediators and is elevated in patients with clinical sepsis, it should be considered a central mediator of sepsis. Some of the disparity in clinical reports regarding the frequency of elevation of plasma TNFα in plasma of patients with sepsis and the ability of elevated plasma concentrations to predict outcome is related to the use of different assays (with different sensitivities) to detect TNFα concentrations. In addition, there is considerable variation in patient populations and timing of plasma TNFα measurements in these studies. Given these considerations, TNFα concentrations are usually elevated in patients with sepsis compared with other critically ill patients and these concentrations are higher in patients with septic shock; however, persistently elevated TNFα concentrations may be better predictors of outcome than single measurements.

INTERLEUKIN 1 (IL-1)

IL-1 is the term used for two related proteins, IL-1α and IL-1β. Both molecules activate the same IL-1 receptors and therefore share various biological activities. IL-1 is synthesized by mononuclear phagocytes, polymorphonuclear leucocytes and other cell types and affects a wide variety of tissues [16]. IL-1β is the predominant form of this mediator produced by endotoxin-stimulated human monocytes and detected in the plasma of septic animals. Both IL-1α and IL-1β mimic many of the biological activities of TNFα. Infusion of either form of IL-1 into humans causes fever, haemodynamic abnormalities, anorexia, malaise, arthralgia, headache and neutrophilia [16, 56]. IL-1β is increased in humans after infusion of endotoxin, although at lower concentrations than TNFα [6, 28]. Like TNFα, IL-1β activates the production of other cytokines, including IL-6, IL-8 and TNFα. Further evidence of a primary role of IL-1β in sepsis syndrome is provided by studies using IL-1ra to block the biological activity of exogenous and endogenous IL-1β [15]. For example, prior treatment with IL-1ra decreased the mortality of rabbits treated with endotoxin [42]. In addition, Fischer and colleagues [20] reported that IL-1ra treatment reduced the production of IL-1, IL-6 and IL-8 (but not TNFα), and improved survival after *E. coli* infusion in baboons.

IL-1β is not normally present in human plasma, but has been detected in the plasma of patients with sepsis. McAllister and colleagues [38] reported cytokine measurements from three patients who developed sepsis after being transfused with packed erythrocytes contaminated with Gram-negative bacteria. These patients had detectable IL-1β that peaked by 4 h and subsequently returned to normal in the two survivors, but remained elevated in the non-surviving patient for 22 h. Plasma IL-1β can be detected in a minority of patients with sepsis but seems to be a measure of the severity of sepsis. Endo and colleagues [18] found that plasma IL-1β was elevated in only two of 40 patients with sepsis alone, but 15 of 22 patients with septic shock had elevated IL-1β concentrations. Casey, Balk and Bone [7] reported that 37% of patients with sepsis had initially detectable plasma concentrations of IL-1β, that the mean IL-1β concentration was higher in patients with sepsis than critically ill patients without sepsis and that the initial IL-1 plasma concentration did not predict mortality in patients with sepsis. A recent study by Goldie and colleagues [24] detected IL-1β in plasma of 29% of 146 patients with severe sepsis but no correlation with mortality was found. Taken together, the available studies of IL-1β in human sepsis show that IL-1β is elevated in plasma of some patients with sepsis. Initial plasma IL-1β concentration may correlate with severity of sepsis, but no convincing independent association with mortality has been found.

Distal cytokines

IL-6

IL-6 is a 21-kDa glycoprotein produced by many cell types, including lymphocytes, fibroblasts and monocytes. IL-6 has a variety of biological effects, including activation of B- and T-lymphocytes, induction of acute phase protein production in the liver, and modulation of haematopoiesis [4]. In addition, IL-6 can activate the coagulation system [65] and function as a pyrogen [14]. *In vitro*, IL-6 suppresses the production of TNFα and IL-1β [1, 48]. The exact role of IL-6 in sepsis is uncertain. Infusion of IL-6 into experimental animals does not result in a sepsis-like state [44]. Xing and colleagues [72] transfected the IL-6 gene into rat lung tissue and found that expression of IL-6 resulted in lung lymphoid hyperplasia and acute phase protein production by the liver, without any other untoward effects.

Experimental injections of endotoxin or bacteria result in detectable plasma IL-6, with peak concentrations occurring subsequent to peak TNFα and IL-1 concentrations. After i.v. endotoxin injection into healthy human volunteers, Kuhns, Alvord and Gallin [32] found that plasma TNFα peaked at 1.5–2 h, whereas IL-6 peaked at 4 h. In baboons treated with sublethal doses of endotoxin or *E. coli*, plasma TNFα concentrations peak at 1–2 h, followed by IL-6 at approximately 3 h [11, 68]. In these same studies, lethal doses of *E. coli* caused peak plasma concentrations of TNFα at 2–3 h and peak IL-1β concentrations at 3–5 h, but IL-6 concentrations were still increasing 6–8 h after injection.

The appearance of plasma IL-6 in sepsis may be related directly to TNFα and IL-1 production. In mice, IL-1 and TNFα synergize to increase IL-6 production, and the production of IL-6 after endotoxin injection can be inhibited by prior treatment with anti-TNFα antibodies [52]. In addition, TNFα antibodies and IL-1ra attenuate IL-6 production in bacteraemic baboons [20, 21].

Although IL-6 is an integral part of the cytokine cascade, its individual role in the pathobiology of sepsis is unclear. In experimental animals, IL-6 blockade has not resulted in consistent benefit. Libert and colleagues [33] showed anti-IL-6 antibodies and antibodies to the IL-6 receptor offered some protection against lethal doses of TNFα in mice, but this protection could be overcome with higher doses of TNFα. In chimpanzees treated with endotoxin, monoclonal anti-IL-6 antibodies did not affect plasma TNFα concentrations, IL-8 concentrations, neutrophilic leucocytosis or neutrophil degranulation [65]. The major effect of anti-IL-6 antibody treatment in this study was to attenuate endotoxin-induced activation of coagulation.

IL-6 concentrations correlate more closely than other cytokines with severity and outcome of human sepsis, despite the fact that the role of IL-6 in this syndrome is not well defined. Plasma IL-6 may simply be a marker for activation of the cytokine cascade, and thus may reflect the association of host inflammatory response and disease severity. Hack and colleagues [26] reported that 32 of 37 patients admitted to an intensive care unit with sepsis had elevated IL-6 concentrations. IL-6 concentrations were higher in patients with septic shock, and IL-6 concentrations correlated with mortality. Damas and colleagues [12] reported serial measurements of TNFα and IL-6 in 40 patients with sepsis. In this study, peak serum IL-6 concentrations correlated with peak TNFα concentrations, APACHE II scores, and increased mortality. Several other studies [5, 7, 18, 24, 61] have confirmed this relation between IL-6 concentrations and the severity and outcome of sepsis. In addition, Moscovitz and colleagues [41] reported that in 100 patients admitted as emergencies and suspected of having bacteraemia, plasma IL-6 concentrations predicted bacteraemia and subsequent death from infection. IL-6 plasma concentration may also reflect severity of other diseases such as alcoholic hepatitis [54]. Based on the available information on IL-6 in human disease, plasma IL-6 concentration in sepsis appears to be a good indicator of activation of the cytokine cascade and predicts subsequent organ system dysfunction and death.

IL-8

IL-8 is a small, basic protein which belongs to the chemokine gene family of cytokines. IL-8 is produced by mononuclear phagocytes, polymorphonuclear leucocytes, endothelial cells, epithelial cells and a variety of mesothelial cell types in response to various stimuli, including endotoxin, IL-1 and TNFα. The primary function of IL-8 is to activate and chemoattract neutrophils to sites of inflammation. In addition, basophils and T-lymphocytes are attracted by nanomolar concentrations of IL-8, and IL-8 has been implicated an angiogenic factor [31].

When injected intradermally into humans, IL-8 induces a time-dependent perivascular neutrophil influx [62]. I.v. injection of IL-8 into baboons causes no haemodynamic abnormalities and no detectable production of TNFα, IL-1β or IL-6 [69]. Transient granulocytopenia followed by granulocytosis occurs, but no significant tissue neutrophilic inflammation or injury. In human and primate models of sepsis, plasma IL-8 levels are detectable following endotoxaemia, and the kinetics mirror IL-6 plasma concentrations [32, 68]. In baboons, plasma IL-8 peaks after 2.5–3 h after a sublethal dose of endotoxin, whereas TNFα concentrations peak at 1 to 2 h [68]. Like IL-6, IL-8 production in sepsis appears to be activated by TNFα. Redl and colleagues [46] showed that treatment of baboons with anti-TNFα antibodies before *E. coli* infusion results in significantly decreased plasma IL-8 concentrations. In human sepsis, Marty and colleagues [37] and Hack and colleagues [27] have reported that plasma IL-8 concentrations are elevated in patients with sepsis and that higher concentrations correlate with mortality.

IL-8 may be important in mediating some of the organ dysfunction, including adult respiratory distress syndrome (ARDS), that occurs as a consequence of sepsis syndrome. IL-8 is present in bronchoalveolar lavage (BAL) fluid of patients with ARDS. BAL IL-8 concentration correlates with BAL neutrophil count and increased mortality in patients with ARDS [9, 40]. In a rabbit ischaemia-reperfusion lung injury model, where tissue injury is mediated at least partially by neutrophils (similar to ARDS), anti-IL-8 antibodies have been shown to have a protective effect [50]. Taken together, these data indicate that the function of IL-8 in sepsis is likely to be recruitment and activation of neutrophils in specific sites which can lead to tissue injury.

Soluble receptors and receptor antagonists

SOLUBLE CYTOKINE RECEPTORS

Soluble cytokine receptors have been described for TNFα, IL-1β and IL-6. Currently, the greatest amount of information regarding soluble cytokine receptors in sepsis syndrome examines the role of soluble TNFα receptors (sTNFR) [10]. Almost no data exist which define the role of the sIL-1R, sIL-6R or other soluble receptors in human sepsis syndrome. Soluble receptors have been described for both the p75 (sTNFR-p75) and p55 TNF (sTNFR-p55) receptor (also called the type I or type A and type II or type B TNFR, respectively). These soluble receptors are produced apparently by proteolytic cleavage of the extracellular binding domain of the TNF receptors from the cell surface. Since these sTNFR retain the ability to bind TNFα, they can modulate the actions of this cytokine. The proportion of free TNFα and TNFα bound to sTNFR exists in equilibrium and this balance may determine the bioactivity of a given TNFα concentration.

Plasma sTNFR concentrations are present in normal humans and are released in excessive amounts into the circulation in response to endotoxaemia. In healthy human volunteers, endotoxin injection results in a 4–5-fold increase in sTNFR concentration by 3 h, with peak plasma concentrations 10 times that of TNFα [57]. Van Zee and colleagues [67] showed that the kinetics of TNFα production and sTNFR shedding are different in experimental models of sepsis. In these experiments, plasma TNFα concentration peaked 1 h after endotoxin infusion, but plasma sTNFR concentration peaked at 3 h. In human sepsis, sTNFR is increased and correlates with severity of illness and mortality. Ertel and colleagues [19] reported that plasma concentrations of both species of sTNFR were increased in patients with sepsis and correlated with APACHE II score, multiple organ failure score and mortality. These findings were supported by Goldie and colleagues [24] who found that higher plasma sTNFR concentrations predicted mortality in a group of patients with severe sepsis.

The role of sTNFR in sepsis is incompletely understood, as is the relation between elevated plasma sTNFR and increased mortality. Plasma sTNFR concentrations may simply be a marker for the exaggerated inflammatory state and not reflective of TNFα/sTNFR ratios in certain tissues or at critical times. Alternatively, the TNFα-sTNFR complex may serve as a slow release reservoir of TNFα, which could perpetuate the inflammatory response.

IL-1 RECEPTOR ANTAGONIST (IL-1RA)

IL-1ra was first identified as a 23 kDa protein purified from the urine of patients with monocytic leukaemia [49]. The amino acid sequence for this protein is 26% homologous to IL-1β and 19% homologous to IL-1α. IL-1ra blocks IL-1 activity by competing for binding to type 1 and type 2 IL-1 receptors without causing signal transduction [16]. IL-1ra can attenuate endotoxin effects in animal models of sepsis [20, 42]. In human volunteers, plasma IL-1ra concentrations are increased after endotoxin injection, with peak concentrations at 3–4 h [32]. In humans with sepsis, IL-1ra is present in plasma at markedly higher concentrations than IL-1, but its function in this setting is uncertain. Gardlund and colleagues [22] reported that 11 of 13 patients with septic shock had plasma IL-1ra/IL-1β ratios > 2000. van Deuren and colleagues [66] found significantly higher plasma IL-1ra concentrations in patients with meningococcaemia and shock than in patients with meningococcal meningitis alone. Goldie and colleagues [24] reported that plasma IL-1ra concentrations were elevated in patients with severe sepsis, but concentrations did not correlate with outcome in this group of patients.

Counter-inflammatory cytokines

IL-10

In addition to pro-inflammatory cytokines, cytokines with predominantly counter-inflammatory actions have been identified. IL-10 was first described as a product of TH2 lymphocytes that inhibits cytokine production by activated macrophages. *In vitro,* IL-10 can inhibit production of TNFα, IL-1, IL-6 and IL-8 [35]. Gerard and colleagues [23] showed that treatment of mice with IL-10 before endotoxin could prevent endotoxin-induced mortality and diminish plasma TNFα release. Additionally, Rogy and colleagues [47] demonstrated that transfecting mice with the human IL-10 gene resulted in transgene expression in the animals, and that these animals were protected from lethal doses of endotoxin. Finally, treatment of mice with anti-IL-10 antibodies has been shown to increase endotoxin-induced TNFα release and worsen mortality [35].

Recent human studies have shown that IL-10 is detectable in plasma of patients with sepsis [13, 25, 34, 66]. van Deuren and colleagues [66] found significantly higher plasma IL-10 concentrations in patients with septic shock compared with patients without shock. This finding was corroborated by Marchant and colleagues [34], who reported that higher IL-10 concentrations were present in patients with septic shock than in patients with sepsis alone. The importance of IL-10 in human sepsis is currently uncertain.

Anticytokine treatment strategies

With increasing evidence that activation of the cytokine cascade is of critical importance in determining the pathobiology of sepsis, there has been increasing enthusiasm for treatments to interrupt this cascade. Current human trials utilizing anticytokine treatments for sepsis have been reviewed recently by Suffredini [59]. Three anticytokine treatment strategies have been evaluated in humans with sepsis: (1) blocking endotoxin effects with polyclonal or monoclonal endotoxin antibodies, (2) blocking TNFα effects with anti-TNFα antibodies or with TNF receptor constructs, and (3) blocking the actions of IL-1 with IL-1ra.

To date, human trials of anticytokine therapy have been relatively disappointing with regard to identifying treatments to improve survival in sepsis. The reason for this lack of efficacy is unclear. Certainly the timing and dose of these interventions may be critical, since these treatments affect proximal steps in the cytokine cascade. Once the cascade is activated, interventions to decrease proximal cytokine actions may be insufficient to improve outcome significantly. In addition, cytokines have redundant and overlapping functions so that blocking the production or action of single cytokines may not affect outcome. Finally, blocking cytokine production may inhibit host defence functions that are critical for recovery from sepsis. There may be a balance between excessive inflammation which causes tissue injury and inadequate inflammatory response which compromises host defence functions.

Therapies designed to modulate activation of the cytokine cascade are certainly attractive and may eventually prove beneficial in sepsis. A better approach than current treatment strategies may be to modulate the cytokine cascade by targeting elements that control production of both proximal and distal cytokines, such as the transcription factor NK-κB. Counter-inflammatory molecules such as IL-10 may also be capable of globally modifying the cytokine cascade. Regardless of the therapeutic approach, future studies for the treatment of sepsis should be conducted as prospective, randomized placebo-controlled, multi-centre clinical trials [3]. These trials will require close cooperation between basic scientists, clinicians and pharmaceutical companies.

Summary

Sepsis is a constellation of clinical signs and symptoms resulting from excessive systemic host inflammatory response to infection. This inflammatory response is largely mediated by cytokines, which are released into the systemic circulation. Plasma concentrations of specific cytokines, TNFα, IL-1β, IL-6 and IL-8 are frequently elevated in human sepsis and cytokine concentrations correlate with severity and outcome of sepsis. In addition to pro-inflammatory cytokines, soluble cytokine receptors, cytokine receptor antagonists and counter-inflammatory cytokines are also produced in large quantities in patients with sepsis; however, the specific role of these molecules in sepsis remains undefined. A complex interaction of cytokines and cytokine-neutralizing molecules probably determines the clinical presentation and course of sepsis. Intervening in this sequence of events to modify the host inflammatory responses may prove to be a beneficial treatment strategy for sepsis, but currently tested anticytokine therapies have been largely unsuccessful.

References

1. Aderka D, Le J, Vilcek J. IL-6 inhibits lipopolysaccharide-induced tumour necrosis factor production in cultured human monocytes, U937 cells and mice. *Journal of Immunology* 1989; **143**: 3517–3523.
2. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; **20**: 864–974.
3. Bernard GR. Sepsis trials: intersection of investigation, regulation, funding, and practice. *American Journal Respiratory and Critical Care Medicine* 1995; **152**: 4–10.
4. Borden EC, Chin P. Interleukin-6: a cytokine with potential diagnostic and therapeutic roles. *Journal of Laboratory and Clinical Medicine* 1994; **123**: 824–829.
5. Calandra T, Gerain J, Heumann D, Baumgartner J-D, Glauser MP and the Swiss-Dutch J5 Immunoglobulin Study Group. High circulating levels of interleukin-6 in patients with septic shock: evolution during sepsis, prognostic value, and interplay with other cytokines. *American Journal of Medicine* 1991; **91**: 23–29.
6. Cannon JG, Tompkins RG, Gelfand JA, Michie HR, Stanford GG, van der Meer JWM, Endres S, Lonnemann G, Corsetti J, Chernow B, Wilmore DW, Wolff SM, Burke JF, Dinarello CA. Circulating interleukin-1 and tumour necrosis factor in septic shock and experimental endotoxin fever. *Journal of Infectious Diseases* 1990; **160**: 79–84.
7. Casey LC, Balk RA, Bone RC. Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. *Annals of Internal Medicine* 1993; **119**: 771–778.
8. Chapman PB, Lester TJ, Casper ES, Gabrilove JL, Wong GY, Kempin SJ, Gold PJ, Welt S, Warren RS, Starnes HF, Sherwin SA, Old LJ, Oettgen HF. Clinical pharmacology of recombinant tumour necrosis factor in patients with advanced cancer. *Journal of Clinical Oncology* 1987; **5**: 1942–1951.
9. Chollet-Martin S, Montravers P, Gibert C, Elbim C, Desmonts JM, Fagon JY, Gougerot-Pocidalo MA. High levels of interleukin-8 in the blood and alveolar spaces of patients with pneumonia and adult respiratory distress syndrome. *Infection and Immunity* 1993; **61**: 4553–4559.
10. Christman JW, Blackwell TS. Paradoxical molecular regulation of soluble cytokine receptors in human sepsis. In: Debets R, ed. *Methods in Molecular Biology: Protocols in Human Cytokine Research.* Totowa, NJ: The Humana Press, 1996 in press.
11. Creasey AA, Stevens P, Kenney J, Allison AC, Warren K, Catlett R, Hinshaw L, Taylor FB. Endotoxin and cytokine profile in plasma of baboons challenges with lethal and sublethal *Escherichia coli*. *Circulatory Shock* 1991; **33**: 84–91.
12. Damas P, Ledoux D, Nys M, Vrindts Y, De Groote D, Franshimont P, Lamy M. Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Annals of Surgery* 1992; **215**: 356–362.
13. Derkx B, Marchant A, Goldman M, Bijlmer R, van Deventer S. High levels of interleukin-10 during the initial phase of fulminant meningococcal septic shock. *Journal of Infectious Diseases* 1995; **171**: 229–232.
14. Dinarello CA. The endogenous pyrogens in host defense interactions. *Hospital Practice* 1989; **24**: 111–128.
15. Dinarello CA, Thompson RC. Blocking IL-1: interleukin 1 receptor antagonist *in vivo* and *in vitro*. *Immunology Today* 1991; **12**: 404–410.
16. Dinarello CA. Interleukin-1 and interleukin-1 antagonism. *Blood* 1991; **77**: 1627–1652.
17. Emerson TE, Lindsey DC, Jesmok GJ, Duerr ML, Fournel MA. Efficacy of monoclonal antibody against tumour necrosis factor alpha in an endotoxemic baboon model. *Circulation Shock* 1992; **38**: 75–84.

18. Endo S, Inada K, Inoue Y, Kuwata Y, Suzuki M, Yamashita H, Hoshi S, Yoshida M. Two types of septic shock classified by the plasma level of cytokines and endotoxin. *Circulatory Shock* 1992; **38L** 264–274.
19. Ertel W, Scholl FA, Gallati H, Bonaccio M, Schildberg FW, Trentz O. Increased release of soluble tumour necrosis factor receptors into blood during clinical sepsis. *Archives of Surgery* 1994; **129**: 1330–1336.
20. Fischer E, Marano MA, Van Zee KJ, Rock CS, Hawes AS, Thompson WA, DeForge L, Kenney JS, Remick DG, Bloedow DC, Thompson RC, Lowry SF, Moldawer LL. Interleukin 1 receptor blockade improves survival and hemodynamic performance in *Escherichia coli* septic shock, but fails to alter host responses to sublethal endotoxemia. *Journal of Clinical Investigation* 1992; **89**: 1551–1557.
21. Fong Y, Tracey KJ, Moldawer LL, Hesse DG, Manogue KB, Kenney JS, Lee AT, Kuo C, Allison AC, Lowry SF, Cerami A. Antibodies to cachexin/tumour necrosis factor reduces interleukin-1β and interleukin 6 appearance during lethal bacteremia. *Journal of Experimental Medicine* 1989; **170**: 1627–1633.
22. Gardlund B, Sjolin J, Nilsson A, Roll M, Wickerts C-J, Wretlind B. Plasma levels of cytokines in primary septic shock in humans: correlation with disease severity. *Journal of Infectious Diseases* 1995; **172**: 296–301.
23. Gerard C, Bruyns C, Marchant A, Abramowicz D, Vanderbeele P, Delvaux A, Fiers W, Goldman M, Velu T. Interleukin-10 reduces the release of tumour necrosis factor and prevents lethality in experimental endotoxemia. *Journal of Experimental Medicine* 1993; **177**: 547–550.
24. Goldie AS, Fearon KC, Ross JA, Barclay GR, Jackson RE, Grant IS, Ramsay G, Blyth AS, Howie JC. Natural cytokine antagonist and endogenous antiendotoxin core antibodies in sepsis syndrome. The Sepsis Intervention Group. *Journal of the American Medical Association* 1995; **274**: 172–177.
25. Gomez-Jimenez J, Martin MC, Sauri R, Segura RM, Estgan F, Ruiz JC, Nuvials X, Boveda JL, Peracaula R, Salgado A. Interleukin-10 and the monocytic/macrophage-induced inflammatory response in septic shock. *Journal of Infectious Diseases* 1995; **711**: 472–475.
26. Hack CE, De Groot ER, Felt-Bersma RJ, Nuijens JH, Strack Van Schijndel RJ, Eerenberg-Belmer AJ, Thijs LG, Aarden LA. Increased plasma level of interleukin-6 in sepsis. *Blood* 1989; **74**: 1704–1710.
27. Hack CE, Hart M, Strack van Schijndel RJM, Eerenberg AJM, Nuijens JH, Thijs LG, Aarden LA. Interleukin-8 in sepsis: Relation to shock and inflammatory mediators. *Infection and Immunity* 1992; **60**: 2835–2842.
28. Hesse DG, Tracey KJ, Fong Y, Manogue KR, Palladino MA jr, Cerami A, Shires GT, Lowry SF. Cytokine appearance in human endotoxemia and primate bacteremia. *Surgery, Gynecology and Obstetrics* 1988; **166**: 147–153.
29. Hinshaw LB, Emerson TE, Taylor FB, Chang ACK, Duerr M, Peer GT, Flournoy DJ, White GL, Kosanke SD, Murray CK, Xu R, Passey RB, Fournel MA. Lethal Staphylococcus aureus-induced shock in primates prevention of death with anti-TNF antibody. *Journal of Trauma* 1992; **33**: 568–573.
30. Johnson J, Meyrick B, Jesmok G, Brigham KL. Human recombinant tumour necrosis factor α induction mimics endotoxemia in awake sheep. *Journal of Applied Physiology* 1989; **66**: 1448–1454.
31. Koch AE, Polverini PJ, Kunkel SL, Harlow LA, DiPietro LA, Elner VM, Elner SG, Strieter RM. Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science* 1992; **258**: 1798–1801.
32. Kuhns DB, Alvord WG, Gallin JI. Increased circulating cytokines, cytokine antagonists, and E-selectin after intravenous administration of endotoxin in humans. *Journal of Infectious Diseases* 1995; **171**: 145–152.
33. Libert C, Vink A, Coulie P, Brouchaert P. Evaraerdt B, van Snick J, Fiers W. Limited involvement of interleukin-6 in the pathogenesis of lethal septic shock as revealed by the effect of monoclonal antibodies against interleukin-6 or its receptor in various murine models. *European Journal of Immunology* 1992; **22**: 2625–2630.
34. Marchant A, Deviere J, Byl B, De Groote D, Vincent JL, Goldman M. Interleukin-10 production during septicaemia. *Lancet* 1994; **343**: 707–708.
35. Marchant A, Bruyns C, Vanderbeele P, Abramowitcz D, Gerard C, Delvauz A, Ghezzi P, Velu T, Goldman M. The protective role of interleukin-10 in endotoxin shock. In: Levin J, Sander JH, van Deventer T, van der Poll AS, eds. *Progress in Clinical and Biological Research: Bacterial Endotoxin: Basic Science to Anti-Sepsis Strategies.* New York: Wiley–Liss, 1994; **388**: 417–423.
36. Martin C, Sauzx P Mege JL, Perrin G, Papazian L, Gouin F. Prognostic value of serum cytokines in septic shock. *Intensive Care Medicine* 1994; **20**: 272–277.
37. Marty C, Misset B, Tamion F, Fitting C, Carlet J, Cavaillon JM. Circulating interleukin-8 concentrations in patients with multiple organ failure of septic and nonseptic origin. *Critical Care Medicine* 1994; **22**: 673–679.
38. McAllister SK, Bland LA, Arduino MJ, Wenger PN, Jarvis WR. Patient cytokine response in transfusion-associated sepsis. *Infection and Immunity* 1994; **62**: 2126–2128.
39. Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, Cerami A, Wolpe SA, Wilmore DW. Detection of circulating tumour necrosis factor after endotoxin administration. *New England Journal of Medicine* 1988; **318**: 1481–1485.
40. Miller EJ, Cohen AB, Nagao S, Griffith D, Maunder RJ, Martin TR, Weiner-Kronish JP, Sticherling M, Christophers E, Matthay MA. Elevated levels of NAP-1/interleukin-8 are present in the airspaces of patients with the adult respiratory distress syndrome and are associated with increased mortality. *American Review of Respiratory Diseases* 1992; **146**: 427–432.
41. Moscovitz H, Shofer F, Mignott H, Behrman A, Kilpatrick L. Plasma cytokine determinations in emergency department patients as a predictor of bacteremia and infectious disease severity. *Critical Care Medicine* 1994; **22**: 1102–1107.
42. Ohlsson K, Bjork P, Bergenfeldt M, Hageman R, Thompson RC. Interleukin-1 receptor antagonist reduces mortality from endotoxin shock. *Nature* 1990; **348**: 550.
43. Pinsky MR, Vincent JL, Deviere J, Alegre M, Kahn RJ, Dupont E. Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. *Chest* 1993; **103**: 565–575.
44. Preiser JC, Schmartz D, van der Linden P, Content J, vanden Bussche P, Buurman W, Sebald W, Dupont E, Pinsky, MR, Vincent JL. Interleukin-6 administration has no acute hemodynamic or hematologic effects in the dog. *Cytokine* 1991; **3**: 1.
45. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. *Journal of the American Medical Association* 1995; **11**: 117–123.
46. Redl H, Schlag G, Ceska M, Davies J, Buurman WA. Interleukin-8 release in baboon septicemia is partially dependent on tumour necrosis factor. *Journal of Infectious Diseases* 1993; **167**: 1464–1466.
47. Rogy MA, Auffenberg T, Espat NJ, Philip R, Remick D, Wollenberg GK, Copeland EM 3rd, Moldawer LL. Human tumour necrosis factor receptor (p55) and interleukin 10 gene transfer in the mouse reduces mortality to lethal endotoxemia and also attenuate local inflammatory responses. *Journal of Experimental Medicine* 1995; **181**: 2289–2293.
48. Schindler R, Mancilla J, Endres S, Ghorbani R, Clark SC, Dinarello CA. Correlations and interactions in the production of interleukin-6 (IL-6), IL-1 and tumour necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood* 1990; **75**: 40–47.
49. Seckinger P, Dayer JM. Interleukin-1 inhibitors. *Annals of the Institute Pasteur/Immunology* 1987; **138**: 461.
50. Sekido N, Mukaida N, Harada A, Nakanishi I, Watanabe Y, Matsushima K. Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8. *Nature* 1993; **365**: 654–657.
51. Selby P, Hobbs S, Viner C, Jackson E, Jones A, Newell D, Calvert AH, McElwain T, Fearon K, Humphreys J, Shiga T. Tumour necrosis in man: clinical and biological observations. *British Journal of Cancer* 1987; **56**: 803–808.
52. Shalaby MR, Waage A, Aarden L, Espevik T. Endotoxin, tumour necrosis factor-α and interleukin 1 induce interleukin 6 production *in vivo. Clinical Immunology and Immunopathology* 1989; **53**: 488–498.

53. Sherman ML, Spriggs DR, Arthur KA, Imamura K, Frei III E, Kufe DW. Recombinant human tumour necrosis factor administered as a five-day continuous infusion in cancer patients: Phase I toxicity and effects on lipid metabolism. *Journal of Clinical Oncology* 1988; **6**: 344–350.
54. Sheron N, Bird G, Goka J, Alevander G, Williams R. Elevated plasma interleukin-6 and increased severity and mortality in alcoholic hepatitis. *Clinical and Experimental Immunology* 1991; **84**: 449–453.
55. Siebenlist U, Franzoso G, Brown K. Structure, regulation, and function of NF-κB. *Annual Review of Cell Biology* 1994; **10**: 405–455.
56. Smith J, Urba W, Steis R, Janik J, Fenton B, Sharfman W, Conlon K, Sznol M, Creekmore S, Wells N, Elwood L, Keller J, Hestdal K, Ewel C, Rossio J, Kopp W, Shimuzut M, Oppenheim J, Longo D. Interleukin-1 alpha: results of a phase I toxicity and immunomodulatory trial. *American Society of Clinical Oncology* 1990; **9**: 717.
57. Spinas GA, Keller U, Brockhaus M. Release of soluble receptors for tumour necrosis factor (TNF) in relation to circulating TNF during experimental endotoxinemia. *Journal of Clinical Investigation* 1992; **90**: 533–536.
58. Strieter RM, Kunkel SL, Bone RC. Role of tumour necrosis factor-alpha in disease states and inflammation. *Critical Care Medicine* 1993; **21**: S447–463.
59. Suffredini AF. Current prospects for the treatment of clinical sepsis. *Chest* 1994; **22**: S12–S18.
60. Suffredini AF, Fromm RE, Parker MM, Brenner M, Kovacs JA, Wesley RA, Parrillo JE. The cardiovascular response of normal humans to the administration of endotoxin. *New England Journal of Medicine* 1989; **321**: 280–287.
61. Sullivan JS, Kilpatrick L, Costarino AT, Lee SC, Harris MC. Correlation of plasma cytokine elevations with mortality rate in children with sepsis. *Journal of Pediatrics* 1992; **120**: 510–515.
62. Swenssen O, Schubert C, Christophers E, Schroder JM. Inflammatory properties of neutrophil-activating protein-1/interleukin 8 (NAP-1/IL-8) in human skin: a light- and electronmicroscopic study. *Journal of Investigation Dermatology* 1991; **96**: 682–689.
63. Tracey KJ, Fong JY, Hesse DG, Manogue KR, Lee AT, Kuo GC, Lowry SF, Cerami A. Anti-cachetin/TNF monoclonal antibodies prevent septic shock during lethal bacteremia. *Nature* 1987; **330**: 662–664.
64. van der Poll T, Buller HR, ten Cate HT. Activation of coagulation after administration to TNF to normal subjects. *New England Journal of Medicine* 1990; **322**: 1622–1627.
65. van der Poll T, Levi M, Hack CE, ten Vate H, van Deventer SJ, Eerenberg AJ, de Groot ER, Jansen J, Gallati H, Buller HR, ten Cate JW, Aarden LA. Elimination of interleukin 6 attenuate coagulation activation in experimental endotoxemia in chimpanzees. *Journal of Experimental Medicine* 1994; **179**: 1253–1259.
66. van Deuren M, van der Ven-Jongekrijg J, Bartelink AKM, van Dalen R, Sauerwein RW, van der Meer JWM. Correlation between proinflammatory cytokines and antiinflammatory mediators and the severity of disease in meningococcal infections. *Journal of Infectious Diseases* 1994; **172**: 433–439.
67. Van Zee KJ, Kohno T, Fischer E, Rock CS, Moldawer LL, Lowry SF. Tumour necrosis factor soluble receptor circulate during experimental and clinical inflammation and can protect against excessive tumour necrosis factor α *in vitro* and *in vivo*. *Proceedings of National Academy of Sciences USA* 1992; **89**: 4845–4849.
68. Van Zee KJ, DeForge LE, Fischer E, Marano MA, Kenney JS, Remick, Lowry SF, Moldawer LL. IL-8 in septic shock, endotoxemia, and after IL-1 administration. *Journal of Immunology* 1991; **146**: 3478–3482.
69. Van Zee KJ, Fischer E, Hawes AS, Hebert CA, Terrell TG, Baker JB, Lowry SF, Moldawer LL. Effects of intravenous IL-8 administration in nonhuman primates. *Journal of Immunology* 1992; **148**: 1746–1752.
70. Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. *Lancet* 1987; **1**: 355–359.
71. Wheeler AP, Jesmok G, Brigham KL. Tumour necrosis factor's effect on lung mechanics, gas exchange and airway reactivity in sheep. *Journal of Applied Physiology* 1990; **68**: 2542–2549.
72. Xing Z, Braciak T, Jordana M, Croitoru K, Graham FL, Gauldie J. Adenovirus-mediated cytokine gene transfer at tissue sites. Overexpression of IL-6 induces lymphocyte hyperplasia in the lung. *Journal of Immunology* 1994; **153**: 4059–4069.

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Nutrition and immunonutrition

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Nosocomial infections are common in critically ill patients and frequently lead to multiple organ failure and death. Such patients may be vulnerable to infection because of deficiency in immune function brought about by severe illness [32, 54, 66]. Requirement for prolonged ventilation is associated with the development of nosocomial pneumonias and sepsis, and the development of weakness and wasting of skeletal and respiratory muscles is a major cause of prolonged weaning from ventilatory support despite resolution of the underlying condition [15]. It is now recognized that nutritional support has a crucial role in maintaining immunological function and in the prevention of muscle wasting during critical illness. Failure to address the issues of muscle wasting and weakness in critical illness leads to delays in mobilization and prolongation of time to recovery [14, 15].

In this article we review recent work which has highlighted the potential importance of the route of administration, the use of specific nutrient substrates and the use of adjuncts to nutrition such as anabolic hormones in maintaining or augmenting immunological function and preventing muscle catabolism in critically ill patients. Nutritional support is a vital component of all preventive therapies available for multiple organ failure in critical illness.

Weight loss and wasting in critical illness

Despite good evidence that nutritional support in certain circumstances leads to reductions in morbidity and mortality [82], increased utilization of nutritional support has unfortunately led to little change in the rapid development of muscle wasting and consequent weakness associated with critical illness. This is important because it has been shown that the degree of weight loss occurring during acute illness is correlated with mortality [20]. Cachexia in critical illness may be explained by the combined effects of malnutrition, immobilization and the hypercatabolic state which occurs after stress, trauma and sepsis. Many patients in the intensive care unit (ICU) are malnourished on admission because of anorexia as the result of illness or fasting in preparation for surgery and this may be exacerbated by delays in commencing nutritional support after ICU admission.

Even hyperalimentation, however, fails to reverse muscle wasting and negative nitrogen balance during critical illness because the metabolic responses to uncomplicated starvation and to stress, trauma and sepsis are quite different. In starvation there is a fall in basal metabolic rate, resting energy expenditure and tissue oxygen consumption. Hepatic glycogen stores are sufficient for 24 h of glycogenolysis and after this a decrease in insulin secretion and increase in glucagon results in lipolysis and hepatic gluconeogenesis. There is then an adaptive phase during which gluconeogenesis falls and ketosis increases, with ketone bodies becoming the fuel for otherwise glucose-dependent tissues. In uncomplicated starvation, therefore, lean body mass is generally preserved until late, fat breakdown being the chief source of calories. The administration of sufficient nutrition will thus convert the starved catabolic patient to an anabolic state.

After stress, trauma or sepsis, however, the hypermetabolic state seen is distinct from that which follows simple starvation and in particular the adaptation to fat metabolism does not occur. There is a significant increase in caloric requirements, with increases in basal metabolic rate and tissue oxygen consumption and consequent negative energy balance. The circulating concentrations of many hormones (for example catecholamines, glucagon, cortisol and growth hormone) and cytokines are increased leading to rapid glycogenolysis, increased hepatic gluconeogenesis and a reduction in lipolysis. The ability to use glucose and fat is impaired and consequently there is an increased dependency on muscle breakdown for fuel. There is weight loss and muscle wasting which leads to an increased loss of nitrogen in the urine. Most of this nitrogen loss originates from muscle proteins because of increases in both whole body protein breakdown and synthesis [75, 80], with breakdown predominating over synthesis [3]. Weight loss of 30 % was common in burns patients before the introduction of routine nutritional support [94]. In sepsis proteolysis can cause nitrogen losses of up to 30 g (represents as much as 800 g muscle mass [52]) per day. Reversal of muscle wasting and negative nitrogen balance in these patients requires control of the effectors of hypermetabolism together with adequate nutritional support. Muscle loss is not prevented by hyperalimentation, however, this leading instead to hepatic steatosis, abnormal liver function and excess carbon

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Key words

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dioxide production which some authors believe may be detrimental to weaning from ventilatory support [24]. Over the past 20 years the energy intake prescribed to critically ill patients receiving parenteral nutrition has fallen, and it appears that the energy requirements of these patients are in fact similar to those of normal healthy subjects [24]. Energy requirements during critical illness have been overestimated in the past because measurements of resting energy expenditure were made at times of peak hypermetabolism and then extrapolated to longer periods, the effect of infused nutrients at time of measurement was not considered, and corrections for pyrexia were made inappropriately [23]. The lower energy requirements of these patients still reflect hypermetabolism, however, but this is balanced by the effects of reduced physical activity. It has now become clear that it is the quality rather than the quantity of nutrients provided that is of most importance in preventing muscle loss and supporting essential body systems such as the immune system during critical illness. In particular, the amino acid glutamine has been recognized to be of importance to muscles, the gut and to the immune system.

Nutritional assessment

A number of variables can be measured to assess a patient's nutritional status. These include serum concentrations of albumin and transferrin, the triceps skinfold thickness and the cutaneous responses to recall antigens [27]. In practice, however, these measurements are relatively insensitive when used for individual patients, and malnourished patients are generally accurately identifiable on the basis of a subjective clinical assessment [20].

Although it is possible to estimate energy requirements using standard equations such as the Harris-Benedict equation or by indirect calorimetry, these measurements are rarely required in the clinical setting. The majority of ICU patients require 25–30 kcal kg^{-1} day^{-1}. Energy intake greater than this may result in complications associated with overfeeding, except in certain situations such as after severe burns, where greater quantities may be required. Protein requirements for catabolic patients are 1.2–2.0 g kg^{-1} day^{-1} if renal function is normal. Additional supplementation does not result in increased protein synthesis and may contribute to uraemia. Protein dose may need alteration in light of changes in renal and hepatic function, as many catabolic patients are unable to utilize administered nutrients efficiently until they are in a recovery phase. A non-protein calorie to nitrogen ratio of between 100:1 and 150:1 must be administered to permit utilization of the protein load for protein synthesis. For patients requiring parenteral feeding it is recommended that dextrose should provide 70–80% of non-protein energy and lipid the rest, despite the concerns about the immunosuppressive effects of lipid emulsions discussed below [43, 73].

Many critically ill patients require fluid restriction as a therapeutic approach, but will often be given large fluid volumes including antibiotics, vasopressors and other drug infusions. One of the problems encountered in administering nutritional support during critical illness is allowing adequate volume to deliver sufficient quantities of energy and protein. In many cases a balance has to be accepted between the desired nutritional intake and the volume space available.

Route of nutrition in critical illness: enteral *vs* parenteral

Along with the move away from hyperalimentation in critical illness, there has been a change in emphasis from parenteral to enteral administration of nutrients. This has been driven by increased understanding of the pathology of nosocomial infections in the critically ill and the role of the gut in their development. Infection is the most common cause of mortality in critically ill patients irrespective of the underlying cause of their critical illness. The development of nosocomial pneumonia is associated with a mortality exceeding 30% [57]. Interest has centred on the gut as a reservoir of bacteria and endotoxin which may be the cause of nosocomial infections and sepsis syndrome [59]. Tracheal and nasogastric intubation, the use of H_2-receptor antagonists as stress ulcer prophylaxis and the cessation of enteral nutrition all predispose to bacterial overgrowth in the upper gastrointestinal tract. It has been demonstrated that bacteria can be isolated from the stomach of critically ill patients some days before their appearance in the tracheal aspirate [5]. Furthermore, gut mucosal atrophy occurs in the absence of enteral feeding because enterocytes normally obtain some of their nutrients directly from the intestinal lumen. Mucosal atrophy may allow translocation of bacteria or endotoxin to the portal circulation. Translocation of bacteria and endotoxin has been shown to occur in animal models of critical illness [96], but has as yet not been convincingly demonstrated to occur in humans. Circumstantial evidence in support of translocation occurring in humans is provided by the demonstration of increased gut permeability after trauma [50], burns [100] and in critical illness [34, 37], and the finding of significant amounts of endotoxin present in the peritoneal cavity and bacteria present within organ specimens from organ donors without intra-abdominal injuries [90]. Interestingly, 95% of the organ donors in this latter study received no feeding. The use of total parenteral nutrition (TPN) is also associated with atrophy of gut-associated lymphoid tissue (GALT) [51]. The translocation of bacteria into the circulation may stimulate macrophages to release cytokines which generate the hypermetabolic response seen in sepsis, and may be responsible for producing hypoxia and multiple organ failure [12].

In addition to these concerns about the inadvisability of substituting TPN for enteral feeds has come evidence that TPN itself has deleterious immunological effects. TPN appears to accentuate the metabolic response to stress, trauma and sepsis by increased pro-inflammatory cytokine and stress hormone release, by the effects of hyperglycaemia and by a specific immunosuppressive effect of lipid emulsions [73]. Omega-6 polyunsaturated fatty acids

(PUFAs) are the form found in Intralipid used in TPN and may have significant immunosuppressive effects, mainly through stimulation of production of prostaglandin E_2. Prostaglandin E_2 has a direct suppressant effect on delayed cell-mediated immunity, suppresses complement synthesis, increases the generation of superoxide radicals and increases suppressor T-cell activity. In addition, omega-6 PUFAs cause increased production of thromboxane A_2 which results in vasoconstriction and thrombosis [1]. TPN also depresses pulmonary macrophage function [81], and depresses local and systemic immune responses to intraperitoneal infection [28, 43]. The use of TPN has been shown to increase the incidence of intra-abdominal abscesses and septic complications after pancreatic resection for malignancy [8], and to increase mortality three-fold in burns patients [38]. In the clinical situation, however, it is likely that the major adverse immunological effect of TPN is due to the cessation of enteral feeding with the consequent development of mucosal atrophy and bacterial overgrowth.

Animal studies have demonstrated that continuous tube feeding started immediately after burn injury reduces the post-burn hypermetabolic response, and prevents the gut mucosal atrophy seen in a comparative delayed enteral feeding group [64]. Enteral feeding resulted in fewer septic complications in high-risk surgical patients [65] and after abdominal trauma [47]. Enteral nutrition has been shown to prevent bacterial and endotoxin translocation in experimental animal models [96], and a recent study in humans has demonstrated a significant decrease in gut mucosal permeability occurring in critically ill patients receiving glutamine supplemented enteral nutrition when compared with a group receiving standard TPN [34].

In addition to providing the mucosa with essential nutrients and preventing the development of mucosal atrophy, the provision of enteral nutrition may also increase gut blood flow. Reduction of oxygen and nutrient delivery to the gut mucosa because of microcirculatory disturbances is thought to be common in sepsis, and may also play a part in the breakdown of the mucosal barrier to bacteria and endotoxins. Enteral feeding has been shown to ameliorate the decrease in splanchnic blood flow associated with the institution of positive end-expiratory pressure ventilation for acute lung injury [74]. This effect may occur even with only small volumes of feed. Enteral feeding also results in improved hepatic synthesis of albumin compared with parenteral nutrition [19].

For a significant benefit to be seen from the use of enteral rather than parenteral feeding the enteral feed must be started as soon as possible after the insult. No difference in infectious complications were seen in head injury patients begun on enteral feeds 5 to 7 days after injury when compared with a group who were given early TPN; however, if the enteral feed was commenced within 3 days of the injury infectious complications were significantly reduced [48]. It is now generally accepted that enteral feeding can be started almost immediately after operation even in patients undergoing abdominal surgery, and in critically ill patients who are sedated, paralysed and ventilated on the ICU. Gastric stasis may be a problem, but this can be overcome by the use of prokinetic agents, nasojejunal tubes or feeding enterostomies.

It is often not possible to achieve comparable energy delivery by the enteral route to that which can be obtained by TPN; however, although TPN guarantees a certain nutrient delivery utilization may be incomplete. TPN will be required in those patients in whom enteral feeding is contraindicated or fails because of malabsorption, ileus or intractable diarrhoea. Supplemental parenteral nutrition may be needed when it is not possible to provide adequate energy enterally. It is likely, however, that if even small amounts of nutrients can be given enterally this will help maintain mucosal integrity, prevent bacterial overgrowth and help maintain splanchnic blood flow.

There is much interest in alterations in the composition of TPN solutions in an attempt to ameliorate some of the adverse effects associated with their use. Glutamine is a non-essential amino acid with poor stability in solution so is not normally included in parenteral feeds. However, in times of physiological stress blood glutamine concentrations decrease and the amino acid may become "conditionally essential". Glutamine is an important nutrient for enterocytes, and parenteral nutrition containing glutamine has been shown to maintain intestinal barrier function in patients with inflammatory bowel disease [89], and maintain intestinal absorptive capacity in a small group of critically ill patients [88]. There is as yet no clinical evidence that glutamine-supplemented TPN reduces morbidity and mortality caused by infection in critical illness however. The molecular mechanism underlying the beneficial effect of glutamine on gut mucosa is not known, but glutamine has been shown to augment heat shock protein messenger RNA and protein expression in rat enteric crypt cells after injury *in vitro* [22]. Heat shock proteins are stress-response genes that protect cells from various injuries. *Escherichia coli* sepsis in rats causes selective damage to enteric crypt cells, and the morphological abnormalities seen can be partially prevented by parenteral administration of glutamine [95]. In health, gut mucosal cells derive glutamine from luminal contents [84]. If enteral nutrition is better than TPN because of its effects on the gut, and addition of glutamine to TPN offsets some of its deleterious effects on the gut, it is tempting to extrapolate this to recommend the inclusion of glutamine in enteral nutrition for critically ill patients. There are as yet, however, no published studies demonstrating increased efficacy of glutamine-enriched enteral nutrition over standard formulas in reducing infectious complications in the heterogeneous intensive care population.

Preventing muscle loss

GLUTAMINE

Protein loss from muscle during critical illness may occur in response to depletion of plasma amino acids (increased demand), or alternatively increased muscle protein turnover may be stimulated by circulating mediators (hormones or cytokines). The loss of muscle protein may have short-term advantages such as providing substrate for the manufacture of acute phase proteins and fuel for more essential body processes. This may include provision of amino acids such as glutamine for protein synthesis within the cells of the immune system and intestine, for repair processes and for hepatic gluconeogenesis. However, consequential plasma glutamine depletion may be central to the failure of traditional nutritional regimes to reverse muscle catabolism in critical illness. Glutamine constitutes 60% of free intracellular amino acids in skeletal muscle [77]. It is the most important carrier of ammonia from the peripheral tissues to the splanchnic area, and serves as an oxidation fuel during cell division [83]. It is also a donor of nitrogen for DNA and RNA synthesis and hence is essential for the proliferation of cells [79]. Glutamine is the principal metabolic fuel of gut mucosal cells [61, 85], lymphocytes and monocytes [2, 7]. Glutamine also has important roles in generation of ammonia by the kidney and in gluconeogenesis in the liver. Lung, adipose tissue and the liver are all sources of glutamine, but skeletal muscle is thought to be the major site of glutamine storage, synthesis and release. Animal and human studies have demonstrated a net flux of glutamine from peripheral to splanchnic tissue with increased hepatic and intestinal uptake after operative stress or in sepsis [21, 83]. In illness glutamine requirements increase markedly [4], and utilization may exceed endogenous production.

If adequate dietary glutamine is not provided net catabolism of skeletal muscle will occur to supply the requirements of glutamine-dependent tissue. Plasma and muscle glutamine concentrations decrease in catabolic states [4, 70, 77]. In patients with sepsis, depleted muscle glutamine was associated with increased concentrations of glutamine precursors [77]. It is therefore suggested that muscle glutamine depletion in illness may be due to both reduced intracellular synthesis and increased efflux to supply glutamine dependent tissues. A positive correlation between glutamine concentration and rate of protein synthesis has been demonstrated in perfused rat skeletal muscle [41, 55], and protein breakdown was inhibited by glutamine in the same model [55]. Recent studies in humans have suggested that addition of glutamine to nutritional regimes may restore depleted plasma and muscle concentrations and improve nitrogen balance in patients with sepsis [77], after bone marrow transplant [101] and after surgery [86]. In addition, the reduction in muscle protein synthesis seen after operation (as assessed by ribosome analysis) was counteracted [36]. Traditionally, glutamine has not been included in parenteral or enteral feeds for critically ill patients because of difficulties with solubility and stability. Heat sterilization causes glutamine to break down to ammonia and pyroglutamic acid. Recent work has demonstrated that degradation is minimized with cold sterilization; however, solubility problems persist. Glutamine in parenteral nutrition requires large volumes which may not be practical for use in critically ill patients. This problem may eventually be overcome by the use of glutamine dipeptides which are soluble in smaller volumes. Until these issues are resolved the addition of glutamine to parenteral nutrition remains essentially a subject for further research.

There are available, however, proprietary preparations of enteral feeds containing glutamine. Unfortunately, there is little work yet published on the efficacy of glutamine-enriched nutrition in heterogeneous groups of critically ill patients. Preliminary results from a randomized study of glutamine-enriched parenteral nutrition in critical illness have been reported [33]. Plasma glutamine concentrations taken before feeding were significantly depressed in both study and control groups in comparison with normal volunteers. Glutamine-enriched feeding (TPN including 25 g glutamine a day) resulted in partial restoration of plasma concentrations towards normal on day 5, significantly different from the control group. Muscle glutamine concentrations were severely depressed in all patients undergoing muscle biopsies before feeding; however, 5 days of glutamine-enriched feeding did not affect muscle glutamine concentrations when compared with the control feeding group. There is still some debate as to the optimum daily amount of glutamine needed to maintain plasma and muscle concentrations during critical illness. Most workers have used 25 g a day, however, Zeigler has reported a series of dose-response studies conducted to evaluate the clinical safety, efficacy and metabolic effect of glutamine-enriched feeding in humans [98]. Glutamine was administered orally and parenterally in two doses (0.285 g kg^{-1} day^{-1} (approximately 20 g day^{-1}) and at 0.57 g kg^{-1} day^{-1} (approximately 40 g day)) to normal volunteers and to patients after bone marrow transplant (parenteral only). In the patient study plasma glutamine decreased from pretreatment concentrations in both control and low-dose glutamine groups over the first 2 weeks, whereas plasma glutamine increased in the high dose group. Muscle glutamine was not studied; however, nitrogen retention was enhanced in the high dose group, there being no difference between the low dose group and control group. It may be that a higher dose of glutamine is required to restore plasma and muscle glutamine concentrations in the critically ill, and the results of further studies are awaited.

It is interesting to note that normally little dietary glutamine reaches the circulation as a substantial amount is utilized by intestinal cells. Consequently, although there are theoretical reasons to believe that glutamine-enriched enteral nutrition may be the optimum nutritional regime to protect the gut in critical illness, it may not be possible to deliver sufficient glutamine via the enteral route to obtain beneficial effects on muscle catabolism or immune function.

OTHER NUTRIENTS AND GROWTH FACTORS

Some other amino acids which, in certain situations may become essential, are also deficient or absent from parenteral nutrition solutions because of their poor stability. These include cysteine and tyrosine. In some patients with liver disease, the hepatic conversion of phenylalanine to tyrosine and methionine to cysteine is inadequate, and unless sufficient cysteine and tyrosine are included in the nutritional regime wasting of lean tissue will occur [78].

The availability of human anabolic hormones synthesized by recombinant techniques has raised interest in their use in the amelioration or prevention of muscle catabolism during critical illness. It has been postulated that derangement of the growth hormone/insulin-like growth factor 1 (IGF-1) axis may partly explain muscle loss and negative nitrogen balance in critical illness. Growth hormone has both direct fuel regulating effects (lipolysis and insulin antagonism) and indirect growth promoting actions (anabolism) which influence amino acid uptake and protein synthesis. Its anabolic actions are mediated through IGF-1, which is secreted principally by cells of the liver under the control of growth hormone, although synthesis may occur in many other tissues. Critically ill patients are relatively resistant to growth hormone, and circulating concentrations of IGF-1 are reduced despite increased basal secretion of growth hormone [76]. Studies of the therapeutic use of growth hormone in seriously ill humans have mainly involved those with burns [102], although recently there have been reports of the use of growth hormone after surgery [62, 63], sepsis [91] and pancreatitis [99]. These studies confirm that a positive nitrogen balance can be promoted, even in the presence of hypocaloric nutrition [42, 58]. After operation protein synthesis is stimulated in patients, along with an increase in the concentration of free glutamine in muscle [35, 53]. It is possible that the effect of growth hormone therapy on muscle protein synthesis is related to preservation of muscle free glutamine concentrations [55]. It is unclear whether the preservation of muscle glutamine is due to decreased efflux from muscle, increased synthesis in muscle or repletion of the plasma pool by increased hepatic or pulmonary release of glutamine [93]. Growth hormone may also have direct effects on immunological function. In a study of daily s.c. injections of growth hormone (GH) after elective cholecystectomy fewer septic complications were reported in the GH group in comparison with placebo-treated controls [63]. Growth hormone administration to critically ill patients does not appear to be associated with any significant adverse effects, and a multicentre trial of its use in critical illness is currently in progress. IGF-1 has also been administered to patients after operation and to critically ill patients without adverse effects, but as yet there is insufficient information on its use therapeutically in these groups.

Nutrition and the immune system

It has long been recognized that immune function is depressed in seriously ill patients [32, 54, 66]. The metabolic response to stress, trauma and sepsis is closely interrelated with the immunological changes seen after such events. Consequently it has been proposed that nutritional support would be likely to improve host defence mechanisms and reduce morbidity. It appears, however, that unless there is severe protein-calorie malnutrition the provision of traditional nutritional support has little effect on immune function. Patients receiving TPN are, in fact, probably more likely to suffer infectious complications [9] for the reasons we have outlined above. Enteral feeding may be beneficial when compared with the parenteral route in preserving immune competence, but recently interest has also centred on the use of specific nutrients which may confer unique immunological benefits. These nutrients include glutamine, arginine, RNA, omega-3 fatty acids and trace metals such as zinc.

GLUTAMINE AND IMMUNONUTRITION

The net flux of glutamine from peripheral to splanchnic tissue seen after operative stress and in sepsis in animal and human studies [21, 83] is thought to occur at least in part in response to increased demand from immunological tissue. Glutamine is utilized at a high rate by lymphocytes [2] and macrophages [67], both as an oxidative fuel and to provide intermediates for synthesis of purine and pyramidine nucleotides which are essential for DNA and RNA synthesis [46]. Lymphocyte and macrophage proliferation depend upon glutamine concentration in culture media [2, 71, 87]. Differentiation of both B- and T-cells cultured *in vitro* [16] and the appearance of interleukins 1 and 2 [10] in cell culture have been shown to be glutamine dependent, as have antibody production and macrophage phagocytic capacity [92]. It appears that the rate of utilization of glutamine by these cells depends upon the external concentration of glutamine. It is possible, therefore, that some of the immune dysfunction seen after stress, trauma and sepsis is due to glutamine deficiency. Increased lymphocyte proliferation and increased macrophage activity have been reported after glutamine feeding in septic rats [49, 95], and in humans glutamine-enriched TPN appeared to maintain immune function after bone marrow transplant in that there was a reduction in incidence of infectious episodes and shorter stay in hospital [101]. There are, as yet, no published studies addressing the effect of glutamine-enriched feedings on immune function during critical illness in humans. Gottschlich and colleagues administered glutamine enterally in varying concentrations to patients for 4 weeks after burn injury and failed to demonstrate any positive benefits; however, the total daily intake of glutamine was not stated [30]. As we have already noted, however, it may not be possible to provide sufficient glutamine by the enteral route to increase plasma concentrations and thus to produce specific changes in immune function during critical illness.

ARGININE, OMEGA-3 FATTY ACIDS AND RNA

Animal studies have supported the use of nutritional supplements such as arginine, omega-3 PUFAs and RNA to boost immune responsiveness after surgery or trauma. There is no published work evaluating the effect of nutrition supplemented with any of these substances alone on infectious morbidity or mortality in patients; however, they are marketed together commercially in an enteral feed (Impact, Sandoz Nutrition, Bern, Switzerland) which has been evaluated in postoperative patients. Arginine is an essential amino acid during growth, and may become essential in catabolic states. Supplementary dietary arginine has been shown to have useful effects on cellular immunity in laboratory animal studies, resulting in increased thymic size, enhanced lymphocyte proliferation to mitogen and alloantigen, augmented macrophage and natural killer cell lysis of tumour targets and increased lymphocyte interleukin 2 production and receptor activity [45]. Arginine is the precursor for nitric oxide which is now recognized to be a ubiquitous cellular messenger with important immune functions. Rats fed an arginine-enriched diet survived longer after an intraperitoneal bacterial challenge than control animals [69], and arginine-enriched TPN improved survival in rats after caecal ligation and puncture [56]. In postoperative cancer patients, diet supplemented with arginine resulted in recovery to baseline levels of the proliferative response of lymphocytes to concanavalin A and phytohaemagglutinin by day 4, and increased responses by day 7. Patients fed a glycine-supplemented diet showed no such recovery of response [17]. Of interest, patients receiving arginine supplemented feeding also had increased IGF-1 concentration and improved nitrogen balance. No differences in infection rates or outcome between groups were seen in this study, however.

Prostaglandin E_2 (PGE_2) is thought to be an important factor in the generalized immunosuppression which follows major injury. Leucocyte function is suppressed by PGE_2 in culture [29], and high concentrations of PGE_2 are found in the serum of burns patients [68]. When PGE_2 production is blocked by administration of indomethacin after major surgery there is restoration of the immune response and decreased opportunistic infections [25]. Omega-3 and omega-6 PUFAs are essential dietary constituents as they are the sole precursors of eicosanoid metabolites, which include prostaglandins, lipoxins, thromboxanes and leukotrienes. If the diet is rich in omega-3 PUFAs there is suppression in the production of a number of dienoic eicosanoid metabolites with increased production of trienoic metabolites which have lower biological potency. Of particular importance, PGE_2 is replaced by PGE_3, TXA_2 by TXA_3 and PGI_2 by PGI_3. Enteral feeds rich in omega-3 PUFAs lead to suppression of PGE_2 production, an action which is probably as effective as pharmacological administration of cyclo-oxygenase inhibitors such as indomethacin.

Guineapigs recovering from burn injury fed an enteral diet rich in omega-3 PUFAs showed improved immune and metabolic function [1]. Improved survival was seen in guineapigs after exposure to endotoxin challenge [60] and in rats after intra-abdominal implant of a faecal agar pellet [6] who were fed with omega-3 PUFAs commencing before the insult. In burns patients omega-3 PUFAs improved survival, reduced infectious complications and diminished immunosuppression secondary to blood transfusion [31]. Some other animal studies have failed to show an advantage of omega-3 PUFAs in sepsis, however, especially when treatment is started after the insult [39]. Blocking the production of PGE_2 may not always be desirable as the precise role of PGE_2 in the immune response after major insult has not been fully defined. In the early stages after trauma or sepsis PGE_2 may actually have advantageous immunomodulatory effects, perhaps through suppression of the release of other cytokines such as tumour necrosis factor (TNF). After these first stages of injury or infection there is at least some evidence that a reduction in PGE_2 levels may reduce immunosuppression [72]. There may also be some disadvantages to the use of omega-3 PUFAs. In addition to reducing PGE_2 activity, TXA_2 activity is also reduced. This eicosanoid is of importance in the maintenance of vascular tone and in platelet aggregation. PGI_3 which is produced rather than PGI_2, however, has similar biological potency and is both an important inhibitor of platelet aggregation and a vasodilator.

Theoretically, therefore, a diet high in omega-3 PUFAs may predispose to vasodilatation and prolonged bleeding times. Indeed, Greenland eskimos, whose diet is high in fish oils rich in omega-3 PUFAs do have a prolonged bleeding time [72]. The risk of platelet dysfunction remains a concern despite there being no demonstrable increase in bleeding times in critically ill patients given omega-3 PUFA diets. Those studies addressing the issue however have only included small numbers of patients. A more serious concern associated with the use of omega-3 PUFAs is the recognition that diets high in PUFAs can lead to generation of lipid peroxides and consumption of the natural free-radical scavenger, vitamin E. Free radicals and lipid peroxides produce cellular and tissue damage, which raises the possibility that the administration of omega-3 PUFAs may exacerbate the pathological processes associated with the development of multiple organ failure. It is not known whether these concerns are valid in clinical use, or whether any potential increase in lipid peroxide stress could be prevented by concomitant vitamin E administration.

Dietary RNA may be necessary to maintain normal immune function. Nucleotides increase protein synthesis, and are involved in the regulation of several T-cell-mediated immune responses [11]. In an animal model, administration of RNA significantly improved host immune responsiveness and host survival to a septic challenge whereas a diet free of nucleotides resulted in decreased interleukin 2 production, decreased cell-mediated immunity, decreased allograft rejection and reduced resistance to infection [26]. Heyland, Cook and Guyatt, however, in a review of the evidence from all published studies concluded that there is as yet little evidence to support the use of dietary RNA supplementation to prevent infectious complications in critically ill patients [39]. Impact, the commercially available enteral feed supplemented with RNA, arginine and omega-3 PUFAs together has been evaluated in postoperative surgical patients. Nitrogen balance was greater, lymphocyte responsiveness restored, and infectious and wound complications reduced (11% *vs* 37%) in patients given Impact when compared with a group receiving a standard diet after surgery for upper gastrointestinal malignancy; however, the Impact group received a higher daily nitrogen intake [18]. Mean length of hospital stay was also reduced for patients in the supplemented group (16 *vs* 20 days). In another study involving post-surgical patients receiving Impact *vs* an isonitrogenous control diet, T-lymphocyte counts, B-lymphocyte indices, mean immunoglobulin M and G concentrations and mean interferon-gamma after phytohaemagglutinin stimulation were higher in the supplemented group [44]. Cerra and colleagues randomized critically ill trauma patients to Impact or a standard feed and demonstrated greater immune cell proliferative responses *in vitro* [13]. There were no differences in infections or mortality; however, the sample size was small. In a much larger group of critically ill patients Bower, Lavin and LiCari failed to demonstrate a reduction in the overall number of infections in the Impact-treated group, although the number of urinary tract infections was reduced [7]. Length of stay in the ICU was significantly shorter in those patients receiving Impact. Impact appears, therefore, to have some immunological advantages over standard feeds; however, further controlled trials of its use in critically ill patients are needed.

OTHER 'IMMUNONUTRIENTS'

Zinc has an important role in the maintenance of immune function, in promotion of wound healing and in maintenance of intestinal mucosal integrity. Zinc deficiency is associated with reduced concentrations of IGF-1 and reduced rates of protein synthesis [40]. In certain conditions, zinc deficiency is particularly likely. These include severe burns, pancreatitis and patients with excessive loss of gastrointestinal fluid. Urinary excretion of zinc increases with the degree of catabolic stress. Supplemental zinc therapy is recommended during critical illness, guided by regular monitoring of serum zinc concentrations [97].

Some workers have recommended the use of branched chain amino acids or increased doses of antioxidants such as vitamins E and C. There is no work available at present supporting these interventions in critically ill patients [39].

Conclusion

The potential importance of nutritional manipulation in the prevention and management of multiple organ failure occurring as a complication of critical illness is increasingly recognized. Despite much evidence from studies in animal models of sepsis, shock and organ failure, there is as yet little direct evidence in patients with critical illness to support the therapies currently advocated by some workers. Indirect evidence of efficacy is present for some nutritional manipulations from studies in elective surgical patients. The relevance of studies in animal models and in elective patients to patients with critical illness is unclear, however, and large randomized controlled trials are needed before definite pronouncements can be made.

From the evidence that is available can any conclusions be drawn? The enteral rather than parenteral route should be chosen for nutritional delivery in critical illness when possible. The use of enteral nutrition appears to be associated with a reduced incidence of sepsis and likelihood of developing multiple organ failure. At present, there is fairly convincing evidence that glutamine deficiency is a significant problem in critical illness. Addition of glutamine to parenteral nutrition solutions may ameliorate or even prevent the deleterious effects of glutamine deficiency on the gut, the immune system and on muscles. Addition of glutamine to TPN may offset some of the disadvantages demonstrated to be associated with the use of TPN. The efficacy of glutamine-enriched enteral feeding is less clear, however, and unfortunately only enteral glutamine-enriched feeds are widely available commercially. The enteral feed Impact, which contains arginine, omega-3 PUFAs and RNA appears to have useful effects on immunocompetence in elective surgical patients, and it is tempting to extrapolate these to the critically ill. The potential adverse effects of increased lipid peroxide generation in patients with multiple organ failure given omega-3 PUFAs is of concern, however, and the results of formal trials should be awaited before PUFA-enriched feeds are used routinely in the ICU.

There is much exciting work to be done in the field of nutrition and immunonutrition in critical illness, and it is likely that future improvements in intensive care outcomes will depend at least in part upon choice of nutrients and their route of supply.

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References

1. Alexander JW, Saito H, Trocki O, Ogle CK. The importance of lipid type in the diet after burn injury. *Annals of Surgery* 1986; **204**: 1–8.
2. Ardawi MSM, Newsholme EA. Glutamine metabolism in lymphocytes of the rat. *Biochemical Journal* 1983; **212**: 835.
3. Arnold J, Campbell IT, Samuels TA, Devlin JC, Green C, Hipkin L, Macdonald I, Scrimgeour C, Smith K, Rennie M. Increased whole body protein breakdown predominates over increased whole body protein synthesis in multiple organ failure. *Clinical Science* 1993; **84**: 655–661.
4. Askanazi J, Carpentier YA, Mitchelsen CB, Elwyn DH, Furst P, Kantrowitz LR, Gump FE, Kinney JM. Muscle and plasma amino acids following injury. *Annals of Surgery* 1980; **192**: 78–85.
5. Atherton S, White D. Stomach as a source of bacteria colonising the respiratory tract during artificial ventilation. *Lancet* 1978; **2**: 963.
6. Barton RG, Wells, CL, Carlson, A, Singh R, Sullivan JJ, Cerra FB. Dietary omega-3 fatty acids decrease mortality and Kupffer cell prostaglandin E2 production in a rat model of chronic sepsis. *Journal of Trauma* 1991; 31: 768–773.
7. Bower RH, Lavin PT, LiCari JJ. A modified enteral formula reduces hospital length of stay (LOS) in patients in intensive

care units (ICU) [Abstract]. *Critical Care Medicine* 1993; **21** (Suppl): S275.

8. Brennan MF, Pisters PWT, Posner P, Quesada O, Shike M. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. *Annals of Surgery* 1994; **220**: 436–444.
9. Buzby G. Results of the VA cooperative study of preoperative TPN. ASPEN 13th Clinical Congress Proceedings. American Society for Parenteral and Enteral Nutrition. Miami, Florida, 1989.
10. Calder PC, Newsholme EA. Glutamine promotes interleukin-2 production by concanavalin A-stimulated lymphocytes. *Proceedings of the Nutrition Society* 1992; **51**: 105A.
11. Carver JD, Cox WI, Barness LA. Dietary nucleotide effects upon murine natural killer cell activity and macrophage activation. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 18–22.
12. Cerra FB. Hypermetabolism, organ failure and metabolic support. *Surgery* 1987; **101**: 1.
13. Cerra FB, Lehmann S, Konstantinides N, Dzik J, Fish J, Konstantinides F, LiCari JJ, Holman RT. Improvement in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA, and Menhaden oil is independent of nitrogen balance. *Nutrition* 1991; **7**: 193–199.
14. Coakley JH, Nagendran K, Honavar M, Hinds CJ. Preliminary observations on the neuromuscular abnormalities in critically ill patients. *Intensive Care Medicine* 1993; **19**: 323–328.
15. Coakely JH, Nagendran K, Ormerod IEC, Ferguson C, Hinds CJ. Prolonged neurogenic weakness in patients requiring mechanical ventilation for acute airflow limitation. *Chest* 1992; **5**: 1413–1416.
16. Crawford J, Cohen HJ. The essential role of L-glutamine in lymphocyte differentiation in vitro. *Journal of Cell Physiology* 1985; **124**: 275–282.
17. Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, Ruggieri B. Immune and metabolic effects of arginine in the surgical patient. *Annals of Surgery* 1988; **208**: 512–523.
18. Daly M, Lieberman MD, Goldfine J, Shou J, Weintraub F, Rosato EF, Lavin P. Enteral nutrition with supplemental arginine, RNA and omega-3 fatty acids in patients after operation: immunologic, metabolic and clinical outcomes. *Surgery* 1992; **112**: 56–57.
19. De Feo P, Horber FF, Haymond MW. Meal stimulation of albumin synthesis: a significant contributor to whole body protein synthesis in humans. *American Journal of Physiology* 1992; **263**: E794–E799.
20. Detsky AS. Parenteral nutrition—is it helpful? *New England Journal of Medicine* 1991; **325**: 573–575.
21. Deutz NEP, Reijven PLM, Athanasas G, Soeters PB. Postoperative changes in hepatic, intestinal, splenic and muscle fluxes of amino acids and ammonia in pigs. *Clinical Science* 1992; **83**: 607–614.
22. Ehrenfried JA, Chen J, Li J, Evers BM. Glutamine-mediated regulation of heat shock protein expression in intestinal cells. *Surgery* 1995; **118**: 352–357.
23. Elia M. Changing concepts of nutrient requirements in disease: implications for artificial nutritional support. *Lancet* 1995; **345**: 1279–1289.
24. Elia M, Jebb SA. Changing concepts of energy requirements of critically ill patients. *Current Medical Literature: Clinical Nutrition* 1992; **1**: 35.
25. Faist E, Markewitz A, Fuchs D, Lang S, Zarius S, Schildeberg FW, Wachter H, Reichart B. Immunomodulatory therapy with thymopentin and indomethacin. *Annals of Surgery* 1991; **214**: 264–275.
26. Fanslow WC, Kulkarni A, Van Buren CT, Rudolph F. Effect of nucleotide restriction and supplementation on resistance to experimental murine candidiasis. *Journal of Parenteral and Enteral Nutrition* 1988; **12**: 49–52.
27. Forse RA, Christou N, Meakins JL, MacLean JD, Shizgal HM. Reliability of skin testing as a measure of nutritional state. *Archives of Surgery* 1981; **116**: 1284–1288.
28. Gogos CA, Kalfarentzos F. Total parenteral nutrition and immune system activity: a review, *Nutrition* 1995; **11**: 339–346.
29. Goodwin JS, Ceuppens J. Regulation of the immune response by prostaglandins. *Journal of Clinical Immunology* 1983; **3**: 295–315.
30. Gottschlich M, Powers C, Khoury J, Warden G. Incidence and effects of glutamine depletion in burn patients. *Journal of Parenteral and Enteral Nutrition* 1993; **17**: 439.
31. Gottschlich MM, Jenkins M, Warden GD, Baumer T, Havens P, Snook JT, Alexander JW. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 225–236.
32. Green DR, Faist E. Trauma and the immune response. *Immunology Today* 1988; **9**: 253–255.
33. Griffiths RD. Glutamine—parenteral and enteral supplementation for the critically-ill. *Clinical Nutrition* 1995; **14**: 129–137.
34. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *American Journal of Respiratory and Critical Care Medicine* 1995; **152**: 1545–1548.
35. Hammarqvist F, Strömberg C, von der Decken A, Vinnars E, Wernerman J. Biosynthetic human growth hormone preserves both muscle protein synthesis and the decrease in muscle-free glutamine, and improves whole body nitrogen economy after operation. *Annals of Surgery* 1992; **216**: 184–191.
36. Hammarqvist F, Wernerman J, Ali R, von der Decken A, Vinnars E. Addition of glutamine to TPN after elective abdominal surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis and improves nitrogen balance. *Annals of Surgery* 1989; **209**: 455–461.
37. Harris CE, Griffiths RD, Freestone N, Billington D, Atherton ST, Macmillan RR. Intestinal permeability in the critically ill. *Intensive Care Medicine* 1992; **18**: 38–41.
38. Herndon DN, Barrow RE, Stein M, Linares H, Rutan TC, Rutan R, Abston S. Increased mortality with intravenous supplemental feeding in severely burned patients. *Journal of Burn Care and Rehabilitation* 1989; **10**: 309–313.
39. Heyland DK, Cook DJ, Guyatt GH. Does the formulation of enteral feeding products influence the infectious morbidity and mortality rates in the critically ill patient? A critical review of the evidence. *Critical Care Medicine* 1995; **22**: 1192–1202.
40. Jeejeebhoy K. Nutrient requirements and nutrient deficiencies in gastrointestinal diseases. In: Sleisenger M, Fordtran J, Scharschmidt B, Feldman M, eds. *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*, 5th ed. Philadelphia: W B Saunders, 1993: 2017–2047.
41. Jepson MM, Bates PC, Broadbent P, Pell JM, Millward DJ. Relationship between glutamine concentration and protein synthesis in rat skeletal muscle. *American Journal of Physiology* 1988; **255**: E166–172.
42. Jiang ZM, He G-Z, Zhang SY, Wang XR, Yang NJ, Zhu Y, Wilmore DW. Low dose growth hormone and hypocaloric nutrition attenuate the protein-catabolic response after major surgery. *Annals of Surgery* 989; **210**: 513–525.
43. Katz S, Plaisier BR, Folkening WJ, Grosfeld JL. Intralipid adversely affects reticular bacterial clearance. *Journal of Paediatric Surgery* 1991; **26**: 921–924.
44. Kemen M, Senkal M, Homann H-H, Mumme A, Dauphin A-K, Baier J, Windeler J, Neumann H, Zumtobel V. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. *Critical Care Medicine* 1995; **23**: 652–659.
45. Kirk SJ, Barbul A. Role of arginine in trauma, sepsis and immunity. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 226S–229S.
46. Kovacevic Z, McGivan JD. Mitochondrial metabolism of glutamine and glutamate and its physiological significnce. *Physiology Reviews* 1983; **63**: 547–605.
47. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO. Enteral vs parenteral feeding: effects on septic morbidity following blunt and penetrating abdominal trauma. *Annals of Surgery* 1992; **215**: 503–513.
48. Kudsk KA, Minard G. Enteral versus parenteral nutrition

in the critically ill and injured. *Current Opinion in Critical Care* 1995; **1**: 255–260.

49. Kweon MN, Moriguchi S, Mukai K, Kishino Y. Effect of alanylglutamine-enriched infusion on tumour growth and cellular immune function. *Amino Acids* 1991; **1**: 7–11.
50. Langkamp-Henken B, Donovan TB, Pate LM, Maull CD, Fabian TC, Kudsk KA. Increased intestinal permeability following blunt and penetrating trauma. *Critical Care Medicine* 1995; **23**: 660–664.
51. Li J, Kudsk KA, Gocinski B, Langkamp-Henken B, Dent D, Glezer J. Effect of parenteral and enteral nutrition on gut-associated lymphoid tissue. *Journal of Trauma* 1995; **39**: 44–51.
52. Long CL, Crosby F, Geiger JW, Kinney JM. Parenteral nutrition in the septic patient: nitrogen balance, limiting plasma amino acids, and calorie to nitrogen ratios. *American Journal of Clinical Nutrition* 1976; **29**: 380–391.
53. Lundeberg S, Belfrage M, Wernerman J, von der Decken A, Thunell, S, Vinnars E. Growth hormone improves muscle protein metabolism and whole body nitrogen economy in man during a hyponitrogenous diet. *Metabolism* 1991; **40**: 315–322.
54. Maclean LD, Meakins JC, Taguchi K, Duignan JP, Dhillon KS, Gordon J. Host resistance in sepsis and trauma. *Annals of Surgery* 1975; **82**: 207–217.
55. MacLennan PA, Brown RA, Rennie MJ. A positive relationship between protein synthetic rate and intracellular glutamine concentration in perfused rat skeletal muscle. *FEBS Letters* 1987; **215**: 187–191.
56. Madden HP, Breslin RJ, Wasserkrug HL. Stimulation of T-cell immunity by arginine enhances survival in peritonitis. *Journal of Surgical Research* 1988; **44**: 658–663.
57. Malangoni MA, Crafton R, Mocek FC. Pneumonia in the surgical intensive care unit: factors determining successful outcome. *American Journal of Surgery* 1994; **167**: 250–255.
58. Manson JM, Smith RJ, Wilmore DW. Growth hormone stimulates protein synthesis during hypocaloric parenteral nutrition. *Annals of Surgery* 1988; **208**: 136–142.
59. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract: the "undrained abscess" of multiple organ failure. *Annals of Surgery* 1993; **218**: 111–119
60. Mascioli EA, Iwasa Y, Trimbo S, Leader L, Bistrian BR, Blackburn GL. Endotoxin challenge after menhaden oil diet: effect on survival of guinea pigs. *American Journal of Clinical Nutrition* 1989; **49**: 277–282.
61. Matthews DE, Marano MA, Campbell RG. Splanchnic bed utilization of glutamine and glutamic acid in humans. *American Journal of Physiology* 1993; **264**: E848–E854.
62. Mjaaland M, Unnberg K, Ragnar H, Revhaug A. Nitrogen retention caused by growth hormone in patients undergoing gastrointestinal surgery with epidual analgesia and parenteral nutrition. *European Journal of Surgery* 1991; **157**: 21–27.
63. Mjaaland M, Unneberg K, Larsson J, Nilsson L, Revhaug A. Growth hormone after abdominal surgery attenuated forearm glutamine, alanine, 3-methylhistidine and total amino-acid efflux in patients receiving total parenteral nutrition. *Annals of Surgery* 1993; **217**: 413–422.
64. Mochizuki H, Trocki O, Dominioni L, Alexander JW. Reduction of postburn hypermetabolism and catabolism by early enteral feeding. *Annals of Surgery* 1985; **200**: 297–310.
65. Moore FA, Feliciana DV, Androssy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, Kellum JM jr, Welling RE, Moore EE. Early enteral feeding, compared with parenteral, reduces post operative septic complications: the results of a meta-analysis. *Annals of Surgery* 1992; **216**: 172–183.
66. Munster AM. Immunologic response to trauma and burns: an overview. *American Journal of Medicine* 1984; **76**: 142–145.
67. Newsholme P, Gordon S, Newsholme EA. Rates of utilisation and fates of glucose, glutamine, pyruvate, fatty acids and ketone bodies by mouse macrophages. *Biochemical Journal* 1987; **242**: 631–636.
68. Ninnemann JL, Stockland AE. Participation of prostaglandin E in immunosuppression following thermal injury. *Journal of Trauma* 1984; **24**: 201–207.
69. Nirgiotis JG, Hennessey PJ, Andrassy RJ. The effects of an arginine-free enteral diet on wound healing and immune function in the postsurgical rat. *Journal of Paediatric Surgery* 1988; **122**: 939–941.
70. Parry-Billings M, Baigrie RJ, Lamont PM, Morris PJ, Newsholme EA. Effects of major and minor surgery on plasma glutamine and cytokine levels. *Archives of Surgery* 1992; **127**: 1237–1240.
71. Parry-Billings M, Evans J, Calder PC, Newsholme EA. Does glutamine contribute to immunosuppression after major burns? *Lancet* 1990; **336**: 523–525.
72. Peck MD. Omega-3 polyunsaturated fatty acids: benefit or harm during sepsis. *New Horizons* 1994; **2**: 230–236.
73. Pomposelli JJ, Bistrian BR. Is total parenteral nutrition immunosuppressive? *New Horizons* 1994; **2**: 224–229.
74. Purcell PN, Davis K, Branson RD, Johnson DJ. Continuous duodenal feeding restores gut blood flow and increases gut oxygen utilisation during PEEP ventilation for lung injury. *American Journal of Surgery* 1993; **165**: 188–194.
75. Rennie MJ. Muscle protein turnover and the wasting due to injury and disease. *British Medical Bulletin* 1985; **41**: 257–264.
76. Ross RJM, Miell J, Feeman E, Jones J, Mathews D, Preece M, Buchanan C. Critically ill patients have high basal growth hormone levels with attentuated oscillatory activity associated with low levels of insulin-like growth factor-1. *Clinical Endocrinology* 1991; **35**: 47–54.
77. Roth E, Funovics J, Mühlbacher F, Schemper M, Mauritz W. Metabolic disorders in severe abdominal sepsis: glutamine deficiency in skeletal muscle. *Clinical Nutrition* 1982; **1**: 25–41.
78. Rudman D, Kutner M, Ansley J, Jansen R, Chipponi J, Bain RP. Hypotyrosinemia, hypocystinemia and failure to retain nitrogen during total parenteral nutrition of cirrhotic patients. *Gastroenterology* 1981; **81**: 1025–1035.
79. Salzman NP, Eagle Sebring ED. The utilization of glutamine, glutamic acid and ammonia for the biosynthesis of nucleic acid bases in mammalian cell cultures. *Journal of Biological Chemistry* 1958; **230**: 1001–1013.
80. Shaw JHF, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. *Annals of Surgery* 1987; **205**: 288–294.
81. Shou J, Lappin J, Daly JM. Impairment of pulmonary macrophage function with total parenteral nutrition. *Annals of Surgery* 1994; **219**: 291–7.
82. Sibbald WJ, Vincent J-L. Round table conference on clinical trials for the treatment of sepsis. *Critical Care Medicine* 1995; **23**: 394–399.
83. Souba WW, Austgen TR. Interorgan glutamine flow following surgery and infection. *Journl of Parenteral and Enteral Nutrition* 1990; 14 (4(Supplement)): 90S–93S.
84. Souba WW, Herskowitz K, Salloum RM, Chen MK, Austgen TR. Gut glutamine metabolism. *Journal of Parenteral and Enteral Nutrition* 1990; **14** (suppl): 445S–450S.
85. Souba WW, Klimberg VS, Plumley DA, Salloum RM, Flynn TC, Bland KI, Copeland EM. The role of glutamine in maintaining a healthy gut and supporting the metabolic response to injury and infection. *Journal of Surgical Research* 1990; **48**: 383–391.
86. Stehle P, Zander J, Mertes N, Albers S, Puchstein C, Lawin P, Fürst P. Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. *Lancet* 1989; **i**: 231–233.
87. Szondy Z, Newsholme EA. The effect of glutamine concentration on the activity of carbamoyl-phosphate synthase II and on the incorporation of [13H]thymidine into DNA in rat mesenteric lymphocytes stimulated by phytohaemagglutinin. *Biochemical Journal* 1989; **261**: 979–983.
88. Tremel H, Kienle B, Weilemann LS, Stehle P, Furst P. Glutamine dipeptide—supplemented parenteral nutrition maintains intestinal function in the critically ill. *Gastroenterology* 1994; **107**: 1595–1601.
89. van der Hulst R, van Kreel BK, von Meyenfeldt MF, Brummer R-JM, Arends J-W, Deutz NEP, Soeters PB. Glutamine and the preservation of gut integrity. *Lancet* 1993; **341**: 1363–1365.
90. van Goor H, Rosman C, Grond J, Kooi K, Wübbels, Bleichrodt RP. Translocation of bacteria and endotoxin in organ donors. *Archives of Surgery* 1994; **129**: 1063–1066.
91. Voerman HJ, Strack van Schijndel RJM, Groeneveld ABJ,

de Boer H, Nauta JP, van der Veen EA, Thijs LG. Effects of recombinant human growth hormone in patients with severe sepsis. *Annals of Surgery* 1992; **216**: 648–655.

92. Wallace C, Keast D. Glutamine and macrophage function. *Metabolism: Clinical and Experimental 1992;* **41**: 1016–1020.
93. Wernerman J. Effect of growth hormone on muscle and protein in critically ill patients. *Acta Endocrinologica* 1993; **128** (Suppl 2): 19–22.
94. Wolfe R. Nutrition and metabolism in burns. In: *Critical Care: State of the Art*. Vol 7. Fullerton, CA, USA: Society of Critical Care Medicine, 1986: 19–63.
95. Yoshida S, Leskiw MJ, Schluter MD, Bush KT, Nagele RG, Lanza-Jacoby S, Stein TP. Effect of total parenteral nutrition, systemic sepsis, and glutamine on gut mucosa in rats. *American Journal of Physiology* 1992; **263**: E368–E373.
96. Zapata-Sirvent RL, Hansbrough JF, Ohara MM, Rice-Asaro M, Nyhan WL. Bacterial translocation in burned mice after administration of various diets including fiber- and glutamine-enriched enteral formulas. *Critical Care Medicine* 1994; **22**: 690–696.
97. Ziegler T. New developments in specialised nutrition support. In: Bion J, Burchardi H, Dellinger R, Dobb G, eds. *Current Topics in Intensive Care Number 2*. London: W B Saunders, 1995: 144–174.
98. Ziegler TR, Benfell K, Smith RJ, Young LS, Brown E, Ferrari-Baliviera E, Lowe DK, Wilmore DW. Safety and metabolic effects of L-glutamine administration in humans. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 137S–146S.
99. Ziegler TR, Rombeau JL, Young LS, Fong Y, Marano M, Lowry SF, Wilmore DW. Recombinant human growth hormone enhances the metabolic efficacy of parenteral nutrition: a double-blind randomized controlled study. *Journal of Clinical Endocrinology and Metabolism* 1992; **74**: 865–873.
100. Ziegler TR, Smith RJ, O'Dwyer ST, Demling RH, Wilmore DW. Increased intestinal permeability associated with infection in burn patients. *Archives of Surgery* 1988; **123**: 1313–1319.
101. Ziegler TR, Young LS, Benfell K, Scheltinga M, Hortos K, Bye R, Morrow FD, Jacobs DO, Smith RJ, Antin JH, Wilmore DW. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. *Annals of Internal Medicine* 1992; **116**: 821–828.
102. Ziegler TR, Young LS, Ferrari-Balivera E, Dem Ling RH, Wilmore DW. Use of human growth hormone combined with nutritional support in a critical care unit. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 574–581.

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CORRESPONDENCE

Pre-emptive analgesia with NSAID—what does it achieve?

Sir,—We wish to comment on the study of Espinet and colleagues [1] who investigated the combined effect of thoracic extradural local anaesthetic block and administration of diclofenac either 30 min before or 30 min after skin incision on post-hysterectomy pain and analgesic consumption. They found that the timing of analgesia made no difference to pain scores or postoperative analgesic requirements, that is there was no pre-emptive effect of diclofenac and extradural local anaesthesia. They discussed these findings in relation to the known actions of non-steroidal anti-inflammatory drugs (NSAID) in inhibiting peripheral sensitization of the primary afferent nerve terminal and so reducing afferent barrage from the periphery. This afferent barrage contributes to central sensitization in the spinal cord and the degree of central sensitization is said to relate to subsequent pain experience and analgesia [2]. The authors comment that the *lack* of pre-emptive analgesia in their study is at variance with that seen in animal studies using similar paradigms.

While their study was designed carefully to exclude the confounding effects of systemic opioids, nitrous oxide and local anaesthetic test doses, the lack of pre-emptive analgesic effect reported in this study may be explained by central actions of NSAID. In addition, not all types of injury are sensitive to pre-emptive treatment, and under certain circumstances central local anaesthetic block may not prevent the subsequent development of hyperalgesia. These possibilities are discussed below.

It is now well established that prostaglandins contribute not only to peripheral but also to central sensitization, and that NSAID act at central and peripheral sites [3]. In experimental models of central sensitization, intrathecal administration of NSAID results in antinociception [4, 5], and critically, their central action is equally effective whether administered *before or after* the noxious stimulus. This is because they act on intracellular messengers responsible for the maintenance of the persistent nociceptive state in the spinal cord [6]. In humans, systemically administered diclofenac crosses the blood–brain barrier and CSF concentrations may continue to increase for 12 h after a single dose [7]. Therefore, in the study of Espinet and colleagues [1], a central spinal action of diclofenac, reducing central sensitization with equal efficacy either before or after incision, could potentially have obscured any pre-emptive action of extradural bupivacaine. A recent study using pre-emptive *vs* post-injury ketorolac *did* show a small initial opioid sparing effect. However, ketorolac may cross the blood–brain barrier to only a minimal extent and so inhibition of peripheral afferent discharge may not have been obscured by the central actions of the NSAID in this study [8].

Animal studies also show that pre-emptive analgesia may not be effective in all types of injury; Dougherty, Garrison and Carlton [9] have reported that pre-emptive topical administration of lignocaine to the sciatic nerve could ameliorate the development of hyperalgesia in a loose ligation model of nerve injury (a model that shows a marked response to a number of pre-emptive analgesic techniques) [10]. However, Dougherty, Garrison and Carlton [9] also reported that lignocaine showed no pre-emptive effect in a partial transection injury of the sciatic nerve. If different types of injury are differentially sensitive to pre-emptive local anaesthesia, the implications are that some aspects of surgical trauma may not be sensitive to pre-emptive local anaesthetic block. Therefore, differences in operation type and operative technique may contribute to the different outcomes in clinical studies of pre-emptive local anaesthesia.

Furthermore, the *route* of pre-emptive local anaesthetic administration may influence the development of post-injury hyperalgesia. For example, Tverskoy and colleagues [11] reported that spinal anaesthesia with bupivacaine was less effective than local infiltration of bupivacaine in reducing late postoperative wound pain after hernia repair. This is a surprising finding in the light of the common perception among anaesthesists that spinal anaesthesia is more reliable and complete than local infiltration. One initial suggestion given to explain these findings was that topical local anaesthesia may have had an anti-inflammatory effect at the site of the wound [12]. Alternatively, Luo and Wiesenfeld-Hallin have recently reported [13] that while *intrathecal* local anaesthetic initially produces profound block of sensory transmission, as the local anaesthetic wears off, a paradoxical state of spinal hyperexcitability ensues. This may completely mask any previous benefit. More importantly, no subsequent *long-term* behavioural benefit could be shown from pre-emptive *intrathecal* lignocaine, even compared with animals which received no intrathecal lignocaine (although in contrast, topical local anaesthetic to the sciatic nerve has previously been shown to be beneficial with this same nerve injury model [14]). The authors also pointed out that the marked clinical benefit shown by Bach, Noreng and Tjellen in their well known study [15] in amputees was achieved using a combination of extradural local anaesthetic *and* opioid.

Pre-emptive analgesia as a concept has essentially been assumed to relate to inhibition of the afferent barrage, especially the initial "injury discharge" associated with the primary event such as nerve injury. As has been emphasized previously [16], the injury discharge may outlast the treatment and so obscure the benefit implied by some animal studies. Furthermore the following factors: (i) giving drugs that act not only on injury discharge but also on the substrate of the central sensitized state, such as NSAID; (ii) the differential sensitivity of different types of nerve injury to pre-emptive analgesia; and (iii) the recent experimental evidence that intrathecal local anaesthetic *alone* may have little benefit in terms of reducing subsequent central sensitization; all help to explain some of the disappointing findings in clinical studies of pre-emptive analgesia but conversely these same observations will help in the design of better regimens to prevent pain.

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1. Espinet A, Henderson DJ, Faccenda KA, Morrison LMM. Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? *British Journal of Anaesthesia* 1996; 76: 209–213.
2. Munglani R, Hunt S, Jones JG. Spinal cord and chronic pain. In: Kaufmann L, ed. *Anaesthesia Review*. Edinburgh: Churchill Livingstone, 1996; 53–76.
3. McCormack K. Non-steroidal anti-inflammatory drugs and spinal nociceptive processing. *Pain* 1994; 59: 9–43.
4. Malmberg AB, Yaksh TL. Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclo-oxygenase inhibition. *Science* 1992; 257: 1276–1279.
5. Malmberg AB, Yaksh TL. Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1992; 263: 136–146.
6. Coderre TJ, Yashpal K. Intracellular messengers contributing to persistent nociception and hyperalgesia induced by L-glutamate and substance P in the rat formalin pain model. *European Journal of Neuroscience* 1994; 6: 1328–1334.
7. Zecca L, Ferrario P, Costi P. Determination of diclofenac and its metabolites in plasma and cerebrospinal fluid by high-performance liquid chromatography with electrochemical detection. *Journal of Chromatography* 1991; 567: 425–432.
8. Fletcher D, Zetlaoui P, Monin S, Bombart M, Samii K. Influence of timing on the analgesic effect of intravenous ketorolac after orthopaedic surgery. *Pain* 1995; 61: 291–297.
9. Dougherty PM, Garrison CJ, Carlton SM. Differential influence of local anaesthetic upon two models of experimentally induced peripheral mononeuropathy in the rat. *Brain Research* 1992; 570: 109–115.
10. Munglani R, Bond A, Smith G, Harrison S, Elliot PJ, Birch PJ, Hunt SP. Changes in neuronal markers in a mononeuropathic rat model: relationship between neuropeptide Y, pre-emptive drug treatment and long term mechanical hyperalgesia. *Pain* 1995; 63: 21–31.

11. Tverskoy M, Cozacov C, Ayache M, Bradley EL jr, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesthesia and Analgesia* 1990; **70**: 29–35.
12. Woolf CJ, Chong M. Pre-emptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. *Anesthesia and Analgesia* 1993; 77: 362–379.
13. Luo L, Wiesefeld-Hallin Z. Effects of intrathecal local anaesthetics on spinal excitability and on the development of autotomy. *Pain* 1995; **63**: 173–179.
14. Gonzalez-Darder J, Barbera J, Abellan M. Effects of prior anaesthesia on autotomy following sciatic nerve transection in rats. *Pain* 1986; **24**: 87–91.
15. Bach S, Noreng MF, Tjellen NU. Phantom limb pain in amputees during the first 12 months following limb amputation after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301.
16. Munglani R, Jones JG, Hunt S. Pre-emptive analgesia—use of immediate early genes expression as markers of neuronal stimulation. *British Journal of Anaesthesia* 1993; **71**: 458.

Sir,—Thank you for the opportunity to reply to Hudspith and Munglani. On the whole we concur with their comments. The complexity of pain production and the number of mechanisms involved make it difficult to block or reduce the nociceptive input. This almost certainly accounts for the lack of a useful pre-emptive analgesic effect in the clinical setting. It is unlikely that one single analgesic method will be sufficient and we should look towards a multi-modal approach to pain relief/reduction. In a small part this is what we tried to achieve in our study. Further research into this field is needed.

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Cytokine balance and immunosuppressive changes at cardiac surgery

Sir—The study of McBride and colleagues contains much useful information on the immunological changes associated with surgery [1], but omitted several important aspects. We would welcome the authors' comments on the following points.

The authors mention briefly that beta adrenoceptor blocking drugs may alter the pro-inflammatory cytokine response, but the possible effect of other cardiac drugs is not considered. Could calcium channel antagonists also have changed the cytokine response? It has been shown in an animal model that administration of calcium antagonists, either before or after endotoxin administration, exerted a protective effect and decreased mortality [2, 3]. Some cytokines exert their effects by increasing free intracellular calcium, especially IL-4, which is one of the principal cytokines in TH2 lymphocyte development [4]. A decrease in intracellular calcium concentration after calcium channel block may decrease amplification of the initial cytokine signal by interfering with the IP$_3$–calcium–calmodulin pathway. In contrast, it has recently been shown that diltiazem enhanced production of cytokines and maintained immune function after haemorrhage [5]. It seems that cations, and Ca^{2+} in particular, may have important intracellular influences on immune function, and therefore any comparisons between McBride's *in vivo* and *in vitro* cytokine changes must be interpreted with great caution.

In describing the activation of TH2 cells and the increase in IL-10 as key events in an anti-inflammatory response to cardiac surgery, the authors failed to mention that the principal immunological fault after major surgery and trauma is impaired production of TH1 cytokines (interferon gamma, IL-2). These cytokines are crucial for the development of TH1 lymphocytes, which are largely responsible for cell-mediated immunity [6, 7]. Development of TH2 lymphocytes is dependent on the early production of IL-4 (TH2 cytokine) *in conjunction with* down-regulation of interferon gamma and IL-2 [6, 8]. Whether TH2 lymphocyte activity is favoured when TH1 lymphocyte production is suppressed is unclear, but no increase in IL-2 or IL-4 was found during or after cardiopulmonary bypass [9].

The statement that oxpentifylline induces TH2 activity is misleading [10]. This phosphodiesterase inhibitor increases intracellular cAMP concentration which stimulates PGE$_2$ synthesis, resulting in impaired IL-2 synthesis and abnormal TH1 development. Because IL-4 synthesis is not affected, TH2 activity is unaffected. Therefore, preferential TH2 development occurs as a result of inhibition of TH1 lymphocytes [10]. Indeed, failure of IL-2 production is considered to be a major factor in the impaired cell-mediated responses after surgery and trauma [11, 12].

It is clear that there are many factors involved in the immunosuppression after cardiac surgery and the changes in IL-10, IL-1ra and sTNF alpha observed by the authors only play a part.

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1. McBride WT, Armstrong MA, Crockard AD, McMurray TJ, Rea JM. Cytokine balance and immunosuppressive changes at cardiac surgery: contrasting response between patients and isolated CPB circuits. *British Journal of Anaesthesia* 1995; **75**: 724–733.
2. Lee HC, Lum BKB. Protective action of calcium entry blockers in endotoxin shock. *Circulatory Shock* 1986; **18**: 193–203.
3. Bosson S, Kuenzig M, Schwartz SI. Increased survival with calcium antagonists in antibiotic-treated bacteremia. *Circulatory Shock* 1986; **19**: 69–74.
4. Clemens MJ. How do cytokines work? 3.2.5 Inositol phosphates and control of intracellular calcium. In: Clemens MJ, ed. *Cytokines*. Oxford: Bios Scientific Publishers, 1991; 44–46.
5. Meldrum DR, Ayala A, Chaudry IH. Mechanism of diltiazem's immunomodulatory effects after hemorrhage and resuscitation. *American Journal of Physiology* 1993; **265**: C412–421.
6. Faist E, Kupper TS, Baker CC, Chaudry IH, Dwyer J, Baue AE. Depression of cellular immunity after major injury. *Archives of Surgery* 1986; **121**: 1000–1005.
7. Faist E, Markewitz A, Schinkel C, Zimmer S, Ertel W. Trauma-induced alterations of cytokine synthesis patterns: mechanisms and modulatory interventions. In: Oppenheim JJ, Rossio JL, Gearing AJH, eds. *Clinical Applications of Cytokines*. New York: Oxford University Press, 1993; 337–345.
8. O'Riordan M, Mannick JA, Rodrick ML. Cytokine response to surgery, trauma, and burns. In: Oppenheim JJ, Rossio JL, Gearing AJH, eds *Clinical Applications of Cytokines*. New York: Oxford University Press, 1993; 301–305.
9. Steinberg JB, Kapienski DP, Olson JD, Weller JM. Cytokine and complement levels in patients undergoing cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1993; **106**: 1008–1016.
10. Rott O, Cash E, Fleischer B. Phosphodiesterase inhibitor pentoxifylline, a selective suppressor of T helper type-1 but not type-2 associated lymphokine production, prevents induction of experimental autoimmune encephalomyelitis in Lewis rats. *European Journal of Immunology* 1993; **23**: 1745–1751.
11. Chouaib S, Chatenoud L, Klatzman D, Fradelizi D. The mechanisms of inhibition of human IL-2 production. II. PGE$_2$ induction of suppressor lymphocyte. *Journal of Immunology* 1984; **132**: 1851–1857.
12. Aussel MD, Ferrue C, Fehlmann B. Regulation of interleukin-2 synthesis by cAMP in human T-cells. *Journal of Immunology* 1987; **139**: 1179–1184.

Sir,—Sheeran and Hall sought to highlight the potential immunomodulatory effects of calcium antagonists at cardiac surgery. Their comments suggest that calcium antagonists may have influenced the cytokine response.

We have since investigated the balance of pro- and anti-inflammatory cytokines in plasma and bronchoalveolar lavage of children undergoing surgery for congenital heart disease. None of these children received preoperative calcium antagonists. Nevertheless, their cytokine response was similar to that observed in adults, with a phased anti-inflammatory response developing, beginning with IL-10, 10 min after aortic cross-clamp release and followed by IL-1ra and the TNF soluble receptors over the next 24 h. In the absence of calcium antagonists these children were able to mount a phased anti-inflammatory response [1]. The existence of a phased anti-inflammatory cytokine response cannot therefore be attributed to the presence of calcium antagonists.

It is not yet known what factors if any influence the magnitude of the phased anti-inflammatory cytokine response and what clinical significance variations in magnitude of this phased anti-inflammatory cytokine response may have. Our group is actively investigating this, and it is indeed possible that calcium antagonists (including volatile anaesthetic agents) may influence the magnitude of this response.

The cytokine response in patients and the isolated CPB system differed in that there was no increase in anti-inflammatory cytokines *in vitro*. [2]. Because of the known effects of Ca^{2+} on immune function, Sheeran and Hall advise "great caution" in comparison of the cytokine response within patients and the isolated CPB circuits. Cautious comparison of the two systems indicates that the major difference between patients and the isolated CPB circuits is not the absence of calcium antagonists but rather the fact that within the isolated CPB circuit blood does not have an opportunity to escape from the activating non-endothelialized surface of the CPB apparatus and enter the vasculature of the patient. We believe that this is vital to any interpretation of these differences.

Sheeran and Hall described impaired production of TH1 cytokines as "the principal immunological fault" at major surgery and claimed that we failed to mention in our discussion such an "immunological fault". There is nothing new in describing the immune response at cardiac surgery as "being at fault". For years authors have concentrated on the pro-inflammatory response and immunosuppression at cardiac surgery as two aspects of disordered immunological homeostasis. Sheeran and Hall have simply gone further than most in speculating on the "principal" of these so called "immunological faults".

We recommend a fresh approach to investigating immunological change at cardiac surgery. We believe that an alternative and helpful way to investigate the immune changes at elective cardiac surgery is to view the immune changes therein as a model of a successful and indeed appropriate response. Most patients for elective coronary artery bypass grafting (CABG) surgery now go home 5 or 6 days later. Surely this is an example of outstanding immunological success! Let clinical outcome be the arbiter as to which aspects of the immune response at cardiac surgery are at fault.

The cardiac surgical patient with good clinical outcome presents an excellent model for study of a successful immune response. We have been the first to highlight the phased anti-inflammatory response as a possible contributor to this success. Other workers have later described an IL-10 response after cardiac surgery [3]. We have never suggested that the phased anti-inflammatory response which we have described is limited to IL-10, IL-1ra and TNF soluble receptors. In fact it is likely that IL-4, TGF-β and indeed other as yet undiscovered anti-inflammatory cytokines may play an important role in the success of our patients.

Only when the ingredients of a successful immune response such as occurs at cardiac surgery are understood shall we understand when the immune response is "at fault". We believe that it is important to know when the immune response is at fault. This information will only come through comparing the profiles of the immune response of cardiac patients who do well with those who (rarely) go on to develop the systemic inflammatory response syndrome (SIRS) or indeed infective complications such as mediastinitis. This knowledge may then enable us to devise effective strategies in the prevention and early treatment of SIRS in the context of major trauma and non-cardiac surgery. We may even be able to predict those patients at risk of developing severe infective complications.

Sheeran and Hall pointed out that our statement that oxpentifylline induces TH2 activity is misleading. We thank them for this and highlighting that the preferential TH2 development after oxpentifylline treatment is an indirect result of inhibition of TH1 development by the drug.

Immunomodulation in the treatment of SIRS in the ICU has been largely unsuccessful. An air of despondency has descended upon the literature [4]. This may be because we have been too quick to modulate the immune response without fully understanding what is an appropriate response to trauma and sepsis. Perhaps it is time to re-evaluate the cardiac surgical patient as a model of success and then re-design our immunomodulatory strategies accordingly.

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1. McBride WT, Armstrong MA, Gilliland H, McMurray TJ. The balance of pro and anti-inflammatory cytokines in plasma and broncho-alveolar lavage at paediatric cardiac surgery. *Cytokine* 1996 (in press).
2. McBride WT, Armstrong MA, Crockard AD, McMurray TJ, Rea JM. Cytokine balance and immunosuppressive changes at cardiac surgery: contrasting response between patients and isolated CPB circuits. *British Journal of Anaesthesia* 1995; **75**: 724–733.
3. Wan S, Marchant A, DeSmet J-M, Antoine M, Zhang H, Vachiery J-L, Goldman M, Vincent J-L, LeClerc J-L. Human cytokine responses to cardiac transplantation and coronary artery bypass grafting. *Journal of Thoracic and Cardiovascular Surgery* 1996; **111**: 469–477.
4. Petros AJ, Marshall JC, Van Saene HKF. Should morbidity replace mortality as an endpoint for clinical trials in intensive care? *Lancet* 1995; **345**: 369–371.

Perioperative changes in α_1-acid glycoprotein concentrations

Sir,—Booker, Taylor and Saba [1] suggested that preoperative measurement of α_1-acid glycoprotein (AAG) concentration should be performed in all infants undergoing major elective surgery who are expected to receive prolonged bupivacaine infusions in the postoperative period. This is based on concern that bupivacaine toxicity may be related to low plasma concentrations of the drug binding protein. Unfortunately, this concern is, in turn, based on several dubious premises: (1) that plasma protein binding of drugs may have significant pharmacodynamic implications; (2) that changes in protein binding are important clinically for drugs which are highly bound, such as bupivacaine; and (3) that if variations occur in plasma concentrations of AAG, then free plasma concentrations of the drug can vary considerably, whereas the total concentration of the drug in plasma is only slightly affected. To explain these misconceptions is a long story—I refer the authors to a few recent publications [2, 3]. Premise (3) is the incorrect way round; if the *fraction* of bupivacaine bound in plasma changes as a result of a change in AAG concentration, classical pharmacokinetic theory predicts that, in the case of a low hepatic extraction drug such as bupivacaine, *total* plasma drug concentration varies but the *unbound* drug concentration does not. As it is the latter which determines pharmacological effect at steady state, there would be no clinical consequence of a change in AAG concentration. Therefore, on this basis, measurement of this protein would be a waste of time and resources. One *caveat* applies to this conclusion, if AAG concentration decreases in proportion to the degree of hepatic dysfunction, then its measurement may be an indirect predictor of the ability of the liver to clear free bupivacaine by metabolism. However, such an association would be independent of the degree of plasma drug binding.

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1. Booker PD, Taylor C, Saba G. Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery. *British Journal of Anaesthesia* 1996; **76**: 365–368.
2. Tucker GT. Safety in numbers. The role of pharmacokinetics in local anesthetic toxicity. *Regional Anesthesia* 1994; **19**: 155–163.
3. Rolan PE. Plasma protein binding displacement interactions—why are they still regarded as clinically important? *British Journal of Clinical Pharmacology* 1994; **37**: 125–128.

CBF in adults using near infrared spectroscopy (NIRS): potential for bedside measurement?

Sir,—We read with interest the article by Owen-Reece and colleagues [1] and suggest that the findings on correct scaling of NIRS cerebral tissue measurements warrant further discussion.

Comparison between scalp and dural recordings in patients allowed conclusions to be made regarding the percentage of the illuminated tissue volume which was cerebral. Measurement of cerebral blood flow (CBF) with the optodes on the dura compared well with values obtained by invasive techniques, but CBF was underestimated by a factor of 3 with the optodes positioned on the scalp. This can be explained by the cerebral tissues contributing only 30–40 % to the total pathlength. Scalp and skull have been shown to have low blood flow and act as static "deadspace" [2]. The chromophore concentration changes detected by NIRS are mostly cerebral, but they must be seen and expressed as concentration changes occurring in the total illuminated tissue volume, 60–70 % of which is extracerebral in the adult. In a rat model [3] and in neonates [4] it has been postulated that the extracerebral component is less than 20 % of the total optical pathlength and this has been accepted as a minor limitation in these measurements. Previous studies by Elwell and co-workers in adults have alluded to the problem of the relatively small component that the cerebral tissue contributes to the total optical pathlength, but none the less they achieved results for cerebral blood flow comparable with invasive techniques despite using scalp recording [2]. The small cerebral component of the total interrogated volume has major implications for the clinical use of such a system as a small alteration in the cerebral tissue volume has a large effect on the proportions of cerebral and extracerebral tissue in the total illuminated tissue volume and thereby has a major effect on measurements of changes in chromophore concentration. The proportion of cerebral tissue may vary between subjects or even within a subject because of changes in optode/scalp coupling or pathological changes, for example in cerebral oedema when the proportion of brain in the illuminated tissue volume may increase as the brain is forced against the skull. In these circumstances, is the instrument measuring quantified changes in chromophore concentrations occurring in the brain?

It is not specified that figure 1 is a dural recording, but using the values shown to make an estimate of cerebral blood volume this is likely to be the case. If this is a dural recording, the same re-saturation event performed with the optodes placed on the scalp would cause a corresponding change in [HbO$_2$] over the initial 4 s of only 0.6 μmol litre^{-1}. This value would be of a similar magnitude to the baseline variability of the trace.

Desaturation to 95 % is unlikely to prove harmful and has been used in neonatal intensive care practice. However, many patients in whom measurement of CBF would be particularly useful are likely to be at risk from secondary brain injury, for example head-injured patients. We have reservations concerning the clinical acceptance of a desaturation method in this population.

The potential of NIRS to measure cerebral blood flow remains an exciting possibility, but we would question whether a desaturation/resaturation technique in combination with a scalp recording will ever be satisfactory for this purpose in adults.

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1. Owen-Reece H, Elwell CE, Harkness W, Goldstone J, Delpy DT, Wyatt JS, Smith M. Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects. *British Journal of Anaesthesia* 1996; **76**: 43–48.
2. Elwell CE, Cope M, Edwards AD, Wyatt JS, Delpy DT, Reynolds EOR. Quantification of adult cerebral hemodynamics by near-infrared spectroscopy. *Journal of Applied Physiology* 1994; **77**: 2753–2760.
3. Delpy DT, Arridge SR, Cope M, Edwards D, Reynolds EOR, Richardson CE, Wray S, Wyatt J, van der Zee P. Quantitation of pathlength in optical spectroscopy. *Advances in Experimental Medicine and Biology* 1989; **248**: 41–46.
4. Wyatt JS, Cope M, Delpy DT, Richardson CE, Edwards AD, Wray S, Reynolds EOR. Quantification of cerebral blood volume in human infants by near-infrared spectroscopy. *Journal of Applied Physiology* 1990; **68**: 1086–1091.

Sir,—It is true that we have quoted higher values for cerebral blood flow (CBF) elsewhere [1]. These were obtained with a different flow analysis method which is described more fully in that article. Briefly, accumulation of tracer in the brain is biphasic, with a fast and slow component. Thus in that study, CBF was 59 ml 100 g^{-1} min^{-1} in the first 1.5 s with a second peak of 11 ml 100 g^{-1} min^{-1} at 1.5–3 s. These values are similar to those measured by PET.

We decided not to use this type of analysis for our study [2] for two reasons. First, high and low CBF components are not widely used clinically (and are not, in any case, provided by xenon washout and the Kety–Schmidt method). Second, such treatment may confuse a simple "before and after" comparison. We therefore used a single average value calculated over the first 4 s of tracer arrival which is compared more easily with mean CBF measured by other techniques.

We believe that NIRS is able to quantify changes in brain chromophore concentration but these changes must be observed through the "deadspace" of the non-cerebral tissues. It is true that at present we have difficulty in making allowances for this when subsequently handling the data. However, recent computer modelling shows that the cerebral sulci have little effect on the proportion of cerebral tissue illuminated and also that when the optodes are pressed firmly against the scalp, skin blood flow has negligible influence [Delpy D. T., personal communication]. As stated in our article, it is necessary to determine the contribution of extracerebral tissue to the total optical pathlength before further progress is made. Similar modelling work, which we hope will assist in quantifying the effects of extracerebral tissue on near infrared spectroscopic measurements, is also in progress at UCL Department of Medical Physics and Bioengineering.

The authors are correct in interpreting figure 1 as a dural recording and we apologize that this was not made clear. As they imply, the signal-to-noise ratio is a significant problem in measurements made via the scalp and more scalp measurements were rejected than those from dura.

Desaturation–resaturation is unlikely to be harmful for the reasons outlined in the article. However, we agree that it may be preferable to avoid the technique in brain-injured patients. There is a range of cerebral haemodynamic variables which can be observed using NIRS which do not affect arterial oxygen saturation, for example cerebral blood flow measurement using indocyanine green as a tracer, spontaneous cerebral blood volume changes, cerebral vascular response to altered Pa_{CO_2} and mean cerebral saturation.

In view of the progress being made in dealing with the scaling problems of scalp recording and the scope for other cerebral measurements which can be made non-invasively with NIRS, we agree with Hopton, Walsh and Lee that the potential of the technique is exciting. There is a great deal of work still to be done before it is suitable for widespread clinical use.

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2. Owen-Reece H, Elwell CE, Harkness W, Goldstone J, Delpy DT, Wyatt JS, Smith M. Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects. *British Journal of Anaesthesia* 1996; **76**: 43–48.

Hypercoagulability induced by crystalloids

Sir,—The *in vitro* study by Ruttmann, James and Viljoen [1] in which dilution of blood with saline and Haemaccel was shown to render it hypercoagulable, is fascinating reading. Their results not only challenge intuitive assumptions but also have possible implications for our clinical practice and, perhaps more importantly, call into question the methodology of studies designed to assess the effect of regional anaesthesia on the development of postoperative thromboembolic disease (TED).

The authors cite the *in vivo* study of Janvrin, Davies and Greenhalgh [2] in which patients given crystalloid in the perioperative period ("wet" group) had a higher incidence of deep vein thrombosis (DVT) than those who received none ("dry" group). While this is of course no criticism of Ruttmann, James and Viljoen, it is worth pointing out that this frequently cited study involved only 60 patients and its power was in the region of 0.65 [3].

However, the results of the *in vitro* work of Ruttmann, James and Viljoen are compelling, and notwithstanding the above criticism, if the *in vivo* effect is real then this may present a case for the use of the hydroxyethyl starches (HES) where there is a risk of TED, and where plasma volume expansion is required. This colloid, rather than promoting coagulation, prevents it by inducing a mild and transient type-I von Willebrand-like syndrome [4].

Over the years, several studies have demonstrated to varying degrees the effect of extradural and spinal anaesthesia on the reduction in postoperative thromboembolic disease compared with general anaesthesia. The proposed mechanisms whereby this is effected include reduced blood loss and transfusion requirements, reduced stress response and its concomitant procoagulant effect, improved lower extremity blood flow, and reduction in plasminogen activator inhibitor-1 (PAI-1) in those receiving regional anaesthesia [5–7]. In none of these studies was administration of crystalloid and colloid considered to exert any specific effect on coagulation. Only administration of blood was standardized between the groups. In most reports, the design of the study ensured that haemodynamic variables were controlled tightly and this usually implied that those receiving extradural or spinal anaesthesia were preloaded with up to 15 ml kg^{-1} of lactated Ringer's solution and required ongoing plasma volume expansion with this and similar solutions throughout the case and into the postoperative period to achieve "target" haemodynamic values (although the actual volumes were not recorded).

Again, if the procoagulant effect of crystalloid haemodilution is real then it may to some extent mask the beneficial effects of regional anaesthesia if crystalloid is used to preload these patients, and this may provide support for the argument that normotension should be maintained either with vasopressors or HES. Clearly, this work needs to be re-evaluated in the light of any new understanding of the effect of crystalloid haemodilution.

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1. Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *British Journal of Anaesthesia* 1996; 76: 412–414.
2. Janvrin SB, Davis G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery. *British Journal of Surgery* 1980; 67: 690–693.
3. Altman D. *Practical Statistics for Medical Research.* London: Chapman and Hall, 1991.
4. Strauss RG. Review of the effects of hydroxyethyl starch on the blood coagulation system. *Transfusion* 1981; 21: 299–302.
5. Modig J, Borg T, Karlström G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: Role of epidural and general anesthesia. *Anesthesia and Analgesia* 1983; 62: 174–180.
6. Rosenfeld BA, Beattie C, Christopherson R, Norris EJ, Frank SM, Breslow MJ, Rock P, Parker SD, Gottlieb SO, Perler BA, Melville Williams G, Seidler A, Bell W. The effect of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. *Anesthesiology* 1993; 79: 435–443.
7. Davis FM, Laurenson VG, Gillespie WJ, Wells JE, Foate J, Newman E. Deep vein thrombosis after total hip replacement. A comparison between spinal and general anaesthesia. *Journal of Bone and Joint Surgery. British Volume* 1989; 71: 181–185.

Sir,—We agree fully with the comments that our results challenge intuitive assumptions and we agree entirely with the inferences they draw from these results. Furthermore, as Farmery and Kong correctly point out, our results may indeed call into question not only the methodology of studies designed to assess the effect of regional anaesthesia on the development of postoperative thromboembolic disease, but also the methodology of most of the currently quoted studies designed to assess the effect of any of the colloids on coagulation, as the majority use a crystalloid control group.

Whether or not our *in vitro* results can be translated to the clinical situation remains to be resolved. However, we are currently in the process of investigating this effect in human volunteers and the results appear to be consistent with our *in vitro* work. Indeed, using standard tests of coagulation and also thrombelastography, we have been able to further strengthen our hypothesis that haemodilution renders blood hypercoaguable.

We can only agree with the comments of Farmery and Kong that the role of crystalloid solutions needs to be re-evaluated, especially in those circumstances in which the prevention of procoagulant states is desirable.

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BOOK REVIEWS

Fibreoptic Guided Tracheal Intubation—A Practical Approach. N. C. HWANG. Published by McGraw-Hill, Singapore. Pp. 81; illustrated. Price $9.15.

This is a splendid little book which was a pleasure to read. At first sight it appears slim and one wonders how it can cover fibreoptic guided tracheal intubation sufficiently. It appears to be the author's aim to give a "practical approach" and not excess theory. The book is precise, readable and ideal for the trainee who is interested in learning the basics of this technique before gaining any practical experience. For an accomplished operator of the fibreoptic scope, this book is deficient in detail but it does offer some useful guidelines on how to set up a fibreoptic training programme. It also contains good diagrams and photographs but unfortunately they all appear at the end of the book which makes referring to them while reading the text rather tedious. The author has described useful aids for fibreoptic intubations. However, I feel that either diagrams or pictures of the various aids would have been more useful for those who may neither have seen nor used them previously. The chapter on cleaning and maintenance of the fibreoptic scope was well done. However, despite my enthusiasm, the book does have some weak points. The lack of detail in some areas may be misleading to the novice user of the fibreoptic scope, for example administration of local anaesthetic via a cricothyroid puncture is given as a method of anaesthetizing the trachea but there is no mention of complications or suggestions of alternative methods such as using a cannula instead of a needle. The skill acquisition section suggests teaching fibreoptic intubation with patients who are breathing spontaneously (p. 46), again without discussing the drawbacks of this method or alternative methods.

In conclusion, this book is useful for the trainee who wishes to gain a basic knowledge of the fibreoptic scope and fibreoptic intubation at a reasonable price. However, it lacks detail in some key areas.

M. C. Mushambi

Clinical Scenarios in Anaesthesia. W. A. CHAMBERS AND R. E. PATY. Published by Churchill Livingstone, Edinburgh. Pp. 181; indexed. Price £29.50.

The introduction of the simulated clinical into the first part of the "new" FFARCS examination was rightly seen as a major innovation in objectively testing the diagnostic and therapeutic knowledge of candidates. This book has been published to coincide with the change to a two part examination for the diploma of FRCA in which the structured clinical moves to the final part. The book consists of 47 case reports accompanied by follow-on questions, with space for answers, interspersed with further information. A list of recommendations for further reading completes each section. The subjects of the reports are diverse, ranging from the routine (haematemesis, hypercapnia and brachial plexus block) to the esoteric (myotonic dystrophy in pregnancy, aeromedical transport and thymectomy); no claim is made that the whole gamut of the guidelines for the final examination is covered.

Unlike books written specifically as guides to the structured clinical, the format of this book does not follow exactly that of the present examination. The rubric to the majority of examination questions consists of a very short paragraph of history, usually only five or six lines, followed by the results of a physical examination and relevant investigations. The case reports in the book vary from one half to 2.5 pages in length, frequently taking the reader to the end of an operation. In some cases radiographs are pictured, in others clinical photographs and blood chemistry results; there are no electrocardiograph records. This format, while interesting, does not attempt to mimic that of the examination. The vast majority of the current trainees eligible to take the final examination will have seen this format in part I of the present examination; a cohort to whom this format is unfamiliar will soon, however, present themselves.

The questions which follow the scenarios, while covering important topics, frequently do not lead the reader or candidate down a seamless path of thought. Thus a scenario on the conduct of anaesthesia for renal transplantation is followed immediately by a question on the criteria for brainstem death and a report of carotid artery surgery by several questions concerning diabetes. The authors state that the book "sets out to ask more questions than it answers" and "The conduct of the cases is not always the only or necessarily the best technique and the reader is invited to consider whether he or she would have acted differently...". It is doubtful if candidates with less than 3 yr in the specialty are in a position to consider the merits of the treatments as outlined. They might perceive than an induction sequence consisting of thiopentone, gallamine and suxamethonium which leads to anaphylaxis is, to say the least, unusual but they may not be aware that total i.v. anaesthesia with propofol in a 12-yr-old boy undergoing brain biopsy is not a universally accepted technique. To be at their most useful each report might be considered by a tutorial group led by a consultant whose specialty is being addressed. There are inherent dangers in printing sub-optimal treatments in a book targeted directly at inexperienced trainees who may subsequently recall a technique without remembering whence it came and that it was inappropriate.

Moving the structured clinical to the final examination has undoubtedly created a need for books which cover the increased clinical scope of this part of the examination. This book claims to meet this requirement but its format is, in most instances, different from that of the examination. Many of the scenarios are long and detailed, and contain pitfalls for the unwary. Unless potential candidates are guided through the reports, information may be retained which will not stand them in good stead in either the examination or clinical practice. Arguably, readers find that case reports form the most interesting part of medical journals and the scenarios in this book undoubtedly form a very good basis for discussion. It might be suggested that in a second edition the authors might like to consider changing the format of the book either to make it more closely resemble that of the examination or specifically to form the basis for a series of consultant-led tutorials.

D. Saunders

The Cambridge Dictionary of Statistics in the Medical Sciences. B. S. EVERITT. Published by Cambridge University Press, Cambridge. Pp. 277; illustrated. Price £12.95.

All medical researchers require a working knowledge of statistics, but the large number of statistical techniques available, together with recent developments in statistical and computational methods, implies that most individuals will encounter unfamiliar statistical terms in their work. This dictionary addresses this need. Although it was aimed primarily at medical statisticians and students, the author expresses a hope that it will be useful both to medical researchers and clinicians. It comprises 277 pages, and typically there are eight entries per page. There are 70 figures which are used mainly to illustrate graphical techniques, such as the box-and-whisker plot, although probability density functions are also presented graphically.

The type of entry covers a wide range. Medical audit is a defined entry; at another extreme, projection pursuit is included. The coverage tends to be superficial; this is not a textbook and cannot be used as a recipe book to guide the researcher through data analysis. However, the coverage is thorough. In a 6-month period from July to December 1995 all but four statistical tests used in the articles in the *British Journal of Anaesthesia* are included.

The dictionary is extensively cross-referenced, although there is a tendency in some entries for these to be circular. Thus in the excellent entry on "likelihood" there are cross-references to seven other entries, three of which simply lead back to the original. On the whole, abbreviations are dealt with well. For example "least significant difference" appears in the dictionary as a full entry, and this is also referenced as "LSD".

Several of the entries lend themselves to a mathematical treatment and equations are presented. More than 50% of the pages contain some mathematical expressions. The typesetting of equations is clear, with appropriate fonts for operators, brackets and subscripts. The presentation of more mathematical entries assumes a working knowledge of mathematics, including matrix algebra.

The dictionary does not include references to definitive sources. For most entries this is unnecessary, but in some cases it would be helpful. For example, the entry on cluster analysis leads to several related items; a reference to a source which gives a more exhaustive account would help to complete the picture.

Two types of user will benefit from this book. First, the researcher or clinician requiring a summary of a statistical technique that appears in a journal article, and second, the clinician with some knowledge of statistics and a short attention span. There is something of interest on every page; this reviewer enjoyed it very much.

C. J. R. Parker

The Massachusetts General Hospital Hand Book of Pain Management. D. Borsook, A. A. LeBel and B. McPeek (editors). Published by Little, Brown & Co., Boston. Pp. 458; indexed; illustrated. Price £24.00.

There are several large volumes on the management of pain but a niche exists for a small pocket handbook such as this. It is aimed at all health workers who treat patients with chronic pain. It provides an introduction to the management complexities, assessment tools and multiple treatment modalities that are now available.

The book is divided into four sections; the first deals with general issues in pain management and includes good chapters on the neural basis of pain and assessment of pain. The second section deals broadly with diagnostic procedures and therapeutic options and the third section is on the treatment of specific pain syndromes. I was pleased to see that the procedures described were generally undertaken in theatres with monitoring, image intensification and safe recovery facilities. This standard of practice is unfortunately not always achieved everywhere in the UK. The last section is entitled "Special considerations" which, while interesting, could have been incorporated into earlier sections, hence avoiding some repetition.

The handbook is not referenced; however, the suggested reading at the end of each chapter is generally modern and relevant. Two of the seven appendices include useful information such as diagrams of dermatomes and nerve distribution, and the IASP (International Association for the Study of Pain) classification of chronic pain, but the remaining appendices, while interesting, are only of specific relevance to doctors practising in North America.

There are some limitations. It is a multi-author book and as such the quality of chapters is variable. There is inevitably repetition but for newcomers to pain management this can be helpful. The x-rays have not reproduced well but the line diagrams are clear. However, the book reflects North American practice, for example in its emphasis on psychological management (which is not necessarily bad as I believe we tend to be somewhat repressed on this side of the Atlantic!). Recommended drug treatments reflect international differences both in generic and brand names, for example meperidine/pethidine, acetaminophen/paracetamol.

Overall this book presents a rational approach to the multidisciplinary management of pain which is both easy to read and conveniently lightweight. It fills a definite gap in the market and represents good value for those involved in the management of patients with chronic pain and for trainees studying for examinations.

F. A. Campbell

Clinical Anaesthesiology—International Practice and Research—Obstetric Anaesthesia. D. G. Bogod (editor). Published by Baillière Tindall, London. Pp. 174; indexed. Price £30.00.

Many books on anaesthesia become outdated in some aspects at the time of publication. I am pleased to say that this is not the case with this book. There are 10 concise topics, each examining relevant aspects of modern obstetric anaesthetic management, and each by a different author.

Many problems in medicine are caused by ignorance of the aims and problem of other specialties, particularly when those specialties work closely together. To try to improve the anaesthetist's knowledge of obstetrics, the first section is a resumé of modern labour management written by an obstetrician. This section makes particular reference to preterm, breech and multiple deliveries, all of which may involve anaesthetic intervention. Many mothers are now aware of the benefits of extradural analgesia but often question the obstetric anaesthetist or midwife about potential complications. Problems of backache, headache and neurological complications are ably dealt with in a section on the long-term effects of extradurals.

There are sections on new drugs and techniques used in obstetric anaesthetic practice, particularly the use of epispinal techniques and the increased use of spinal and extradural opioids. To complement this there is a section on the neonatal effects of opioids in labour. It states reassuringly that most regimens in common use appear to be safe.

Two other sections complement each other; one a very forthright appraisal of regional techniques for Caesarean section, spinal, extradural and combined techniques, emphasizing the very rare need for general anaesthesia for Caesarean section, the other a section on general anaesthesia for Caesarean section. This is a very thoroughly researched section but in many ways the most disappointing. It is very long-winded and contains at the end a failed intubation drill so long that, if it needed to be referred to in an emergency, I fear the mother's demise long before the end of the algorithm.

Another rather long section deals with audit. Sadly this deviates somewhat from specific obstetric anaesthetic audit and describes anaesthetic audit in general.

There is an excellent section on high-risk pregnancy, with a major emphasis on obesity and asthma, and the management of cardiovascularly and neurologically compromised mothers. The section on feeding in labour gives a clear account of the benefits and potential dangers of feeding mothers in labour. Medico-legal considerations of obstetric anaesthesia are admirably dealt with in the final section in the book.

In short, this is an excellent book and should be of use both to practising obstetric anaesthetists and trainees alike.

R. J. S. Birks

Low Flow Anaesthesia. J. A. Baum and G. Nunn. Published by Butterworth–Heinemann, Oxford. Pp. 208; indexed; illustrated. Price £35.00.

With increasing interest in low flow anaesthesia and the advent of new agents, this books provides a major and timely contribution to the literature. It is a well written and easily read comprehensive review of a potentially difficult subject.

The book successfully covers most aspects of the use of low flow systems. One criticism is that the classification used by the author, while well explained, is confusing. It uses the old terms of semi-open and semi-closed, and may also cause confusion by describing systems such as the Magill and Bain as non-rebreathing systems. The rationale behind the classification given is presented clearly but I am sure it will be a source of annoyance to those accustomed to other classifications. That criticism aside, the book is full of useful information. In particular, several chapters are outstanding. The uptake of anaesthetic agents is well written and easy to follow. Mathematics are present in this book, but are used appropriately, are well diluted by "common sense" text and can be ignored by non-mathematicians without losing the meaning of entire chapters. There is an excellent discussion of the various models of anaesthetic uptake. The chapter on anaesthetic methods for low flow anaesthesia will be useful to all trainees. Of general interest is the exhaustive discussion of the cost implications of low flow anaesthesia.

There is an extremely useful chapter on the newer anaesthetic machines, how they function in relation to flow and the technical requirements of using low flows. The section on monitoring requirements and safety aspects is comprehensive, with lists of the standards and guidelines that are required both at the present time and in the near future. There is a short but informative chapter on substances which accumulate in low flow systems. It is regrettable that at the time this book was written, the newer inhalation agents were only just beginning to become available and there is limited but nevertheless useful discussion of these agents. There is also a very brief section on the use of low flow anaesthesia in paediatric practice.

The information in this book should be available in any department that is intending to use either low or minimal flow anaesthesia. It is a topic that few major texts cover adequately and in which it is almost impossible to find a book that is comprehensive, informative and yet readable. This book achieves these objectives. It is an excellent reference book suitable not only for departments but also for individuals.

N. Soni

Total Burn Care. D. N. HERNDON (editor). Published by Saunders, London. Pp. 597; illustrated; indexed.

This book comprises 597 pages covering 60 chapters. It is written by 82 international authors, mainly from the USA, with a few from the UK, Austria, Australia and Japan, many of whom are well known experts in this field. The book is set out in nine sections.

The first section is a brief introduction of the burn management team and the epidemiology of burns in the USA. It emphasizes the multidisciplinary approach to the care of burns. The second section covers immediate care of burns and includes burn disaster management, pre-hospital care and transportation, and fluid resuscitation. The management of burn disasters highlights important points, including disaster plans, communication, transportation, facilities and staff. Pre-hospital care is well explained but has an unusual heading and layout, that is the management of pain, tetanus immunization and prevention of hypothermia and also gastrointestinal problems are included under one title "Decompression of stomach"! The description of fluid resuscitation is of limited use to the British doctor as it is primarily "American" fluid resuscitation with a brief mention of colloids and no mention of the Muir and Barclay formula, the mainstay of British burn resuscitation. I enjoyed reading the chapter on the pathophysiology of burn shock and burn oedema but unfortunately some of this is repeated under fluid resuscitation and early management.

The third section aims to concentrate on the "Burn wound". This section again suffers from problems of a multi-author book in that there are several repetitions, including that of tables. There is a very brief chapter on anaesthesia for burned patients. A proportion of this includes inhalation injury, a subject which is also covered in three chapters of the next section entitled "Inhalational injury".

The fifth section is on "Responses to injury". This is the largest section and covers a wide range of topics. These include nutritional needs and support, multiple organ failure and its treatment, pathophysiological changes in burns, burn nursing and burns in the elderly and children. It has some good chapters but is a mixture of very different topics. I am not sure if "Responses to injury" is the correct title or if it should have been divided into more than one section. The chapter on renal failure in burned patients should perhaps be incorporated into that on critical care of burn complications as there is a significant amount of overlap in these two chapters.

The sixth section covers non-thermal injuries such as electrical, cold, chemical and radiation injuries, and exfoliative disorders and necrotizing soft tissue infection. These were well written and interesting to read.

The final three sections are on rehabilitation, reconstruction and psychological and social issues. After reading the earlier chapter on anaesthesia for burned patients, I had hoped that anaesthesia for reconstructive surgery would be covered in the section on reconstruction. Unfortunately, this topic has been overlooked and needs to be addressed as it presents anaesthetic problems different from those of the acute phase. Pain response and pain control are covered in the section entitled psychological and social issues. I feel that this chapter, although well written, is misplaced. It gives the impression that pain management is more a long-term problem rather than an early priority in the acute management of burns.

This book has aimed to provide an overall view of total burn management and in so doing has covered a wide range of topics. Most of the chapters are well written but as with all multi-author books, the standard of chapters varies. Anaesthesia does not appear to have been well represented. I believe that the chapters could have been grouped differently to make it an easier reference book. Perhaps the chapters on anaesthesia should have been grouped together to make a better impact. All chapters are well referenced. The summary at the end of each chapter is useful and well done in some sections. The book however, reflects North American practice in many areas, some of which are critical and cannot be easily overlooked by British doctors looking after burned patients. This multi-author book also suffers from a great deal of repetition and will be useful as a reference book, but probably more for surgeons than anaesthetists.

M. C. Mushambi

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

Transoesophageal echocardiography in anaesthesia and intensive care

Transoesophageal echocardiography (TOE) is becoming an increasingly important diagnostic tool in anaesthesia and intensive care. The oesophagus lies immediately posterior to the heart and great vessels and, unlike transthoracic ultrasound, provides an imaging window without interference from intervening structures. Because of this proximity, TOE can use high frequency 5-MHz probes which provide much higher resolution images than those that can be obtained with conventional 2.5–3-MHz transthoracic probes. The uses of TOE have been classified into five main categories [1]:

(1) Imaging of structures which may be inadequately displayed by transthoracic echocardiography, such as the left atrial appendage and the descending thoracic aorta, or when the presence of a prosthetic valve produces an ultrasound shadow.

(2) Diagnosis of conditions in which the superior image quality is vital, for example assessment of endocarditis, intracardiac thrombus, valvular malfunction or aortic dissection. In aortic dissection, TOE has been reported in experienced hands to have a diagnostic sensitivity and specificity of more than 95% [2]. An emerging indication is the routine use of TOE to exclude the presence of left atrial thrombus before elective cardioversion for atrial fibrillation [3].

(3) Ultrasound examination of patients with conditions such as obesity or emphysema which prevent image clarity with transthoracic techniques.

(4) Intraoperative use in both cardiac and non-cardiac surgery to monitor such variables as left ventricular wall motion, effectiveness of valve repair and presence of air embolism without disturbing the surgical field.

(5) Use in the intensive care unit to aid diagnostic conundrums unresolved by other techniques.

The technique was first used in 1976 using a rigid device but standard technology now comprises a biplane probe mounted on a flexible, steerable endoscope imaging in both horizontal and transverse planes, with spectral and colour flow Doppler. Newer multiplane probes allow scanning at any angle through 180°. The technique is invasive, usually carried out under sedation and appears remarkably safe. The overall complication rate is of the order of a fraction of 1% in most series [1]. In one large study group of more than 10000 diagnostic cases, there was one fatality (bleeding tumour infiltrating the oesophagus) and 18 cardiac, pulmonary or bleeding complications [4]. This safety record contrasts markedly with that of gastrointestinal endoscopy [5], perhaps because patients are monitored more intensively and the danger of cardiorespiratory complications are readily apparent. The principal contraindications to TOE are oesophageal tumours, stenoses, diverticulae or varices. Transient bacteraemia has been reported after TOE but antibiotic prophylaxis against endocarditis is currently considered unnecessary.

The TOE probe can be maintained in a stable position allowing beat-by-beat monitoring of cardiac function over prolonged periods. Cardiac output can be measured by Doppler interrogation of aortic blood flow, assessment of preload can be obtained by measurement of left ventricular diastolic dimension and of afterload by calculation of end-systolic wall stress, as described by Greim, Roewer and Esch [6]. Contractility can be assessed by measurement of shortening fraction and ejection fraction, although the dependence of such measures on loading conditions and the geometrical assumptions made with calculation of ejection fraction imply that such measures are of limited value. Determination of the end-systolic left ventricular diameter–pressure relationship in a manner analogous to the pressure–volume relationship may be a better echo-derived index of ventricular function [7].

The ability of TOE to image clearly the endocardial surface allows the technique to be used to monitor global and regional ventricular function in both cardiac and non-cardiac surgical patients in an attempt to detect the occurrence of myocardial ischaemia. Regional wall motion abnormalities occur within seconds of the onset of myocardial ischaemia [8], well before the occurrence of ECG changes or chest pain. Studies in high risk patients have confirmed that TOE is a more sensitive indicator of perioperative myocardial ischaemia than the ECG or haemodynamic monitoring [9, 10]. Whether or not this increased ability to detect perioperative ischaemia results in improved patient outcome is unknown. Compared with preoperative clinical evaluation and standard ECG monitoring, intraoperative TOE failed to add significantly to the ability to identify patients with adverse outcomes caused by myocardial ischaemia [11]. A limitation to monitoring myocardial ischaemia by TOE is that continuous monitoring is usually performed in only one plane and may fail to detect ischaemia in other segments. More importantly, detection of wall movement abnormalities is made by eye so that considerable experience is necessary in image interpretation. This is a particular problem when there are pre-existing wall motion abnormalities, a common feature of patients with ischaemic heart disease. Automated edge detection techniques and the use of cine loops and split screens to allow image comparison may help to overcome such problems. On-line analysis packages are being developed which give continuous information on both measured and derived haemodynamic indices.

The increasing use of mitral and tricuspid valve repair rather than replacement in cases of valvular incompetence has made detailed knowledge of valvular anatomy important in the preoperative assessment of such patients. A TOE study performed before operation or on the operating table before cardiopulmonary bypass allows the surgeon to plan appropriate operative strategies to deal with annular dilatation, cusp retraction, prolapse or perforation. Intraoperative TOE performed after mitral valve repair has been found to identify accurately both satisfactory repairs and those cases with significant residual regurgitation requiring surgical revision [12, 13]. However, assessment of the severity of mitral regurgitation by echo Doppler study is unsatisfactory because colour flow Doppler mapping displays velocity, not total regurgitant flow, and certainly does not provide an "ultrasonic angiogram". The tendency of eccentric regurgitant jets to wrap around the circumference of the left atrium makes underestimation of their severity a common problem. Again, because of the lack of hard numerical data and derived indices, considerable experience in signal interpretation is necessary. Numerous other cardiac surgical procedures have been reported in which intraoperative TOE has been helpful, including myectomy for hypertrophic cardiomyopathy, resection of membranous subaortic stenosis and pulmonary artery and vein anastomosis during lung transplantation.

Although not all editorial writers have been enthusiastic about intraoperative TOE [14–16] and have emphasized the dangers of increased complications and the potential for misdiagnoses, there seems to be a growing acceptance of its value, particularly in valve reconstruction. If TOE is to be brought into routine use as an intra- and postoperative monitoring procedure or in the assessment on the operating table of the results of valvular surgery, two important difficulties arise. The first is the ready availability of equipment, as and when it is needed, and the second is the presence of a well trained operator to interpret the results. The costs of providing an intraoperative TOE service are hard to estimate. A TOE probe alone currently costs in the region of £30000 (and has a limited life span of approximately 500 procedures) and an echo Doppler system approximately £100000. The set-up costs of a dedicated intraoperative unit are consequently substantial, yet sharing time on machines which are in heavy demand for routine diagnostic use inevitably implies that they may be unavailable when required.

Because of their clarity, TOE signals are much easier to interpret than those from transthoracic probes, but nevertheless correct training is essential. To date in the UK, TOE has been largely the preserve of cardiologists but it is impractical to expect them to provide an on-demand intraoperative service. For anaesthetists or surgeons to undertake the responsibility of image interpretation requires an addendum to their normal training programmes. Furthermore, when trained, skills need to be practised to be retained. At present there are no UK guidelines even for the training of cardiologists in TOE but the American Society of Echocardiography published its recommendations in 1992 [17]. Recent preliminary data from Yale indicate that it is not possible during a 3-month cardiac anaesthesia rotation to acquire the standard of skill necessary for independent practice [18]. Although it is recognized that specialized training in TOE for anaesthetists is essential, it is currently difficult to know how it would be best achieved or what numbers and type of case mixed will be required. As with so many things in the UK, success with the technique is likely to come from a small group of enthusiasts who have the energy to raise the money for equipment and the commitment to train correctly, probably in their own time.

The impressive image quality obtainable with TOE and the relative ease with which it can be performed make it likely that it will become an increasingly important diagnostic and monitoring tool during surgery and in the intensive care unit. However, as with any imaging technique, the results obtained will only be as good as the quality of interpretation and this implies appropriate training and continued collaboration with cardiological colleagues, not "having a go" when it becomes a necessity. The potential for misdiagnosis with any imaging technique must never be forgotten.

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References

1. Rafferty TD. *Basics of Transesophageal Echocardiography, Section 1.* New York: Churchill Livingstone, 1995; 2–3.
2. Erbel R, Engberding R, Daniel W, Roelandt J, Visser C, Rennollet H. Echocardiography in diagnosis of aortic dissection. *Lancet* 1989; 1: 457–461.
3. Manning WJ, Silverman DI, Gordon SPF, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *New England Journal of Medicine* 1993; **328**: 750–755.
4. Daniel WG, Erbel R, Kaspar W, Visser CA, Engberding R, Sutherland GR, Grube E, Honruth P, Maisch B, Denning K, Schortl M, Kremer P, Angerman C, Iliceto S, Cortius JM, Mugge A. Safety of transesophageal echocardiography. *Circulation* 1991; **83**: 817–821.
5. Charlton, JE. Monitoring and supplemental oxygen during endoscopy. *British Medical Journal* 1995; **310**: 886–887.
6. Greim CA, Roewer N, Esch JS. Assessment of changes in left ventricular wall stress from the end-systolic pressure-area product. *British Journal of Anaesthesia* 1995; **75**: 583–587.
7. Heinrich H, Foesel TH, Fontaine L, Spilker D, Winter H, Ahnefeld FW. Assessment of contractility changes in humans by transoesophageal echocardiography. The peak systolic pressure and systolic diameter relationship (PSPESDRS). *International Journal of Clinical Monitoring and Computing* 1987; 4: 243–248.

8. Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings. *Journal of the American College of Cardiology* 1985; **5**: 193–197.
9. Smith JS, Cahalan MK Benefiel DJ, Byrd BF, Lurz FW, Shapiro WA, Roizen MF, Bouchard A, Schiller NB. Intraoperative detection of myocardial ischemia in high risk patients: electrocardiography versus two dimensional transesophageal echocardiography. *Circulation* 1985; **72**: 1015–1021.
10. Van Daele M, Sutherland GR, Mitchell MM, Fraser AG, Prakash O, Rulf EN, Roelandt, J. Do changes in pulmonary capillary wedge pressure adequately reflect myocardial ischemia during anesthesia? *Circulation* 1990; **81**: 865–871.
11. Eisenberg MJ, London MJ, Leung J, Browner WS, Hollenberg M, Tubau JF, Tateo IM, Schiller NB, Mangano DT. Monitoring for myocardial ischemia during non-cardiac surgery. *Journal of the American Medical Association* 1992; **268**: 210–216.
12. Sheikh KH, de Bruijn NP, Scott Rankin J, Clements FM, Stanley T, Wolfe WG, Kisslo J. The utility of transeosophageal echocardiography and Doppler color flow imaging in patients undergoing cardiac valve surgery. *Journal of the American College of Cardiology* 1990; **15**: 363–372.
13. Freeman WK, Schaff HV, Khandheria BK Oh JK, Orszulak TA, Abel MD, Seward JB, Tajik AJ. Intraoperative evaluation of mitral valve regurgitation and repair by transesophageal echocardiography: incidence and significance of systolic anterior motion. *Journal of the American College of Cardiology* 1992; **20**: 599–609.
14. Conti R. Transesophageal ultrasound: "invasive" noninvasive cardiology. *Clinical Cardiology* 1991; **14**: 545–546.
15. Goldman M, Mindich B, Nanda N. Intraoperative echocardiography: who monitors the flood once the floodgates are opened? *Journal of the American College of Cardiology* 1988; **11**: 1362–1364.
16. Kaplan J. Monitoring technology: advances and restraints. *Journal of Cardiothoracic and Vascular Anesthesia* 1989; **3**: 257–259.
17. Pearlman AS, Gardin JM, Martin RP, Parisi AF, Popp RI, Quinones MA, Stevenson JG, Schiller NB, Seward JB, Stewart WJ. Guidelines for physician training in transesophageal echocardiography: recommendations of the American Society of Echocardiography Committee for physician training in echocardiography. *Journal of the American Society of Echocardiography* 1992; **5**: 187–194.
18. Konstadt S, Reich D, Raffery TD. Transesophageal echocardiography quality assurance and training: an achievement based approach. *Anesthesia and Analgesia* 1996 (in press).

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CLINICAL INVESTIGATIONS

Single bolus compared with a fractionated dose injection technique of bupivacaine for extradural Caesarean section: effect on uteroplacental and fetal haemodynamic state

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Summary

We studied 26 healthy parturients undergoing elective Caesarean section, allocated randomly to receive extradural block with 0.5% plain bupivacaine in a double-blind manner in either a single bolus or fractionated doses. After a 3-ml test dose, an additional 20 ml of bupivacaine were given over a 5-min period in the single bolus group ($n = 13$) and over a 25-min period in the fractionated dose group ($n = 13$). We studied the effects of bupivacaine on blood flow velocities in the maternal placental and non-placental uterine and fetal umbilical arteries before and four times during establishment of extradural block using a pulsed colour Doppler technique. Median sensory block reached T3 in the single-dose group compared with T4 in the fractionated-dose group. Two subjects in each group required i.v. ephedrine to correct transient hypotension (systolic arterial pressure < 90 mm Hg). Blood flow velocity waveform indices of the uterine and umbilical arteries did not differ significantly within or between groups during the study. There was no significant difference in neonatal outcome, as assessed by Apgar scores and umbilical artery pH values. In conclusion, we observed no deterioration in uteroplacental circulation after administration of a single bolus dose of bupivacaine. (*Br. J. Anaesth.* 1996; **77**: 140–144)

Key words

Anaesthesia, obstetric. Blood, flow, feto–uteroplacental. Anaesthetic techniques, extradural. Anaesthetics local, bupivacaine.

Induction of extradural block with bupivacaine in fractionated doses is a routine technique for elective Caesarean section but it is slow in producing surgical anaesthesia for emergency cases. In order to speed up the onset of sensory block in such acute cases, the local anaesthetic has been given as a single bolus dose via either a needle [1] or catheter [2–4]. This technique may be advantageous, especially in mothers, who already have an extradural catheter *in situ* for pain relief during labour. In previous studies, 0.5% plain bupivacaine given as a slow bolus or in fractionated doses did not cause an increase in uteroplacental and fetal umbilical blood flow resistance [5–7]. In contrast, Alahuhta and colleagues [8] found increased uterine artery Doppler indices, possibly indicating increased vascular resistance, after administration of 20 ml of 0.5% plain bupivacaine as a bolus injection over a 5-min period. Injection of local anaesthetic in fractionated doses via the catheter appeared to be a safer and more efficient technique for extradural Caesarean section than a single dose [9]. In that study, the incidence of hypotension was significantly lower and, after birth, the efficacy of sensory block was greater in the fractionated-dose group than in the single-dose group, while there was no difference in the condition of the neonates, as assessed by Apgar score. Nevertheless, it has been shown that a single bolus dose of bupivacaine does not have any harmful effect on fetal and neonatal outcome, as evaluated by fetal heart rate patterns [10] and Apgar score [11, 12].

There are conflicting results of studies on the effects of extradural anaesthesia on maternal and uteroplacental haemodynamic state, partly because of different injection techniques and doses of local anaesthetics. Therefore, we have compared, in a double-blind, randomized study, the effects of a single bolus and fractionated doses of bupivacaine on maternal uterine and fetal umbilical artery blood flow velocity waveforms using a colour Doppler technique.

Patients and methods

We examined 26 healthy parturients at term (gestational weeks 37–40) undergoing elective Caesarean section because of breech presentation, fetopelvic disproportion or repeat Caesarean section. The study was approved by Oulu University Ethics Committee and informed written consent was obtained from each patient. None of the patients was in labour. Exclusion criteria included multiple gestation and maternal or fetal complications during pregnancy (e.g. pre-eclampsia, diabetes or signs of placental insufficiency).

Patients were given 30 ml of sodium citrate 0.3 mol $litre^{-1}$ orally, 30–60 min before entering the operating theatre, where they were monitored with a three-lead ECG, pulse oximetry and automated non-

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invasive arterial pressure (Cardiocap, Datex, Finland). Oxygen 3 litre min^{-1} was administered via a nasal cannula. A peripheral vein was cannulated for administration of i.v. fluids. With the patient in a right lateral position, the extradural space was identified at the L2–3 or L3–4 interspace with an 18-gauge needle using the loss of resistance technique. A catheter was inserted 3 cm cephalad into the extradural space and secured after negative aspiration for blood and cerebrospinal fluid. Patients were then turned to the supine position with left lateral tilt. Local anaesthetic was not injected. Patients received a preload of Ringer's acetate solution 1 litre over a 15–20-min period. Immediately after preloading, the first Doppler ultrasound recording was performed.

The left and right maternal uterine (main branch) arteries near the cervix before their divisions and the fetal umbilical artery were identified by colour Doppler and blood velocity waveforms recorded by the pulsed Doppler method with a 3.75-MHz sector probe and 120-Hz high-pass filter. Peripheral arterial resistance was expressed in terms of pulsatility index (PI), calculated as PI = (systolic peak velocity − end-diastolic velocity)/mean velocity during cardiac cycle, and measured from the blood velocity waveform profile (the average of three consecutive waveforms).

After the first Doppler recording, patients were allocated randomly to one of two groups of 13 to receive 0.5% plain bupivacaine in a double-blind design, either as a single bolus or in fractionated doses. Randomization was performed in the operating theatre using sealed envelopes. A test dose of bupivacaine 3 ml was injected via the catheter. After 4 min, if there were no signs of subarachnoid or i.v. injection, patients in the single-dose group received a 20-ml (100 mg) bolus dose of bupivacaine over 5 min, and those in the fractionated-dose group an 8-ml (40 mg) dose diluted with 0.9% saline 12 ml (i.e. 20 ml in all) over 5 min. Then, in the latter group, additional bupivacaine doses of 8 ml (40 mg) and 4 ml (20 mg) over 1 min were given 15 and 20 min from the first dose, respectively. In the single-dose group, equal volumes of 0.9% saline were administered in a similar manner. Thus the total amount of bupivacaine given was identical in both groups (23 ml (115 mg)). A Doppler measurement of the same arteries was repeated 5 and 10 min after the first injection of bupivacaine (the second and third Doppler recording) and then 4 min after the subsequent two injections of either bupivacaine or saline (the fourth and fifth Doppler recording). The obstetrician (L. M.) who performed all Doppler recordings and the author (J. K.) who administered all extradural blocks were blinded to the anaesthetic solutions used in the study. The level of sensory block was assessed before surgery, and if below T5, bupivacaine 3–5 ml was given via the catheter.

Maternal heart rate (HR) was monitored continuously and systolic arterial pressure (SAP) recorded every 2 min during the study. During establishment of extradural block, an infusion of a second litre of Ringer's acetate solution was started in both groups to maintain maternal arterial pressure. Hypotension, defined as a decrease in SAP to less than 100 mm Hg or to 80% of baseline, was treated by increasing the rate of crystalloid infusion. If a value of < 90 mm Hg was recorded, ephedrine 5–10 mg was given i.v. The time from uterine incision to delivery was recorded. After delivery, a paediatrician evaluated Apgar scores at 1 and 5 min, and blood samples from a double-clamped umbilical artery were obtained immediately for measurement of acid–base status. The paediatrician also was unaware of the method of bupivacaine injection used for extradural block.

Student's *t* test was used to detect differences in baseline values between the groups. Analysis of variance for repeated measures was used to assess the statistical significance of the differences in maternal haemodynamic variables (HR, SAP and PI) between and within groups. The Greenhouse–Geisser adjustment for multi-sampler asphericity was used to avoid excessive type I error [13]. Values for maternal SAP were computed as percentage changes from baseline values for later analysis. The number of 11 subjects in each group was determined previously to be sufficient to detect, with 80% power and a 5% significance level, a difference of 30% in mean uterine artery PI between the groups [14]. The difference of 30% in the PI values was considered clinically significant. The Mann–Whitney *U* test was used to analyse differences in the height of sensory block between groups. Differences were considered significant if $P < 0.05$. Values are presented as mean (SD, 95% confidence interval (CI) or range) where appropriate.

Results

There was no significant difference in basic clinical data between the groups except for maternal weight. Despite randomization, mothers in the fractionated-dose group weighed significantly more than mothers in the other group (table 1). Changes in mean maternal HR did not differ between ($P = 0.12$) or within ($P = 0.45$) groups during the study (table 2). Similarly, changes in mean maternal SAP did not differ between groups ($P = 0.39$). Mean SAP decreased to a minimum of 86 (95% CI 78–93)% of baseline, that is from 127 (122–132) to 109 (98–119) mm Hg ($P = 0.002$) in the fractionated-dose group, and to 85 (79–92)%, that is from 128 (123–134) to 106 (98–114) mm Hg ($P = 0.001$) in the single-dose group (fig. 1). The lowest values of SAP in each group were observed within 10–20 min after induction of extradural block. In total, hypotension (SAP < 100 mm Hg) occurred in six of 26 patients (23%) (three patients in each group). Of these six subjects, two in each group developed more severe but transient hypotension with SAP < 90 mm Hg, and required ephedrine 5–10 mg i.v. All four patients also required atropine 0.5 mg i.v. for transient bradycardia with HR $\leqslant$ 50 beat min^{-1}. Total requirement for ephedrine was 20 mg in the single-dose and 30 mg in the fractionated-dose group.

Comparison between the right and left uterine arteries showed no difference in PI. Therefore, mean PI from these two vessels was calculated in each

Table 1 Maternal and newborn characteristics (mean (SD or range) or number). UD time = Uterine incision to delivery time

	Fractionated-dose group (n = 13)	Single-dose group (n = 13)	P
Maternal			
Age (yr)	33.7 (26–43)	31.5 (19–46)	0.40
Weight (kg)	83.3 (12.0)	72.5 (10.2)	0.02
Height (cm)	163.1 (8.3)	161.8 (6.7)	0.66
Gestational weeks	38.8 (1.0)	39.0 (0.9)	0.55
Newborn weight (g)	3586 (520)	3565 (503)	0.92
Apgar ≤ 7 (n)			
1 min	1	0	
5 min	0	0	
Umbilical artery pH	7.28 (7.17–7.35)	7.30 (7.19–7.42)	0.26
UD time (s)	75.7 (22.9)	60.1 (16.4)	0.07

Table 2 Maternal heart rate (HR) (mean (95 % CI)) before and after the first dose of bupivacaine solution. No significant differences between groups (ANOVA)

	Fractionated-dose group (n = 13)	Single-dose group (n = 13)
HR (beat min^{-1})		
Before extradural block	77 (68–86)	79 (72–87)
5 min after	73 (66–81)	77 (72–83)
10 min after	79 (70–88)	75 (69–81)
20 min after	75 (70–81)	73 (68–78)
25 min after	81 (74–88)	73 (68–78)

Table 3 Uterine and umbilical artery PI values (mean (95 % CI)) before and after the first dose of bupivacaine solution. No significant differences between groups (ANOVA)

	Fractionated-dose group (n = 13)	Single-dose group (n = 13)
Uterine artery PI		
Before extradural block	0.76 (0.68–0.84)	0.83 (0.64–1.03)
5 min after	0.88 (0.74–1.03)	0.91 (0.75–1.08)
10 min after	0.83 (0.70–0.96)	0.93 (0.68–1.18)
20 min after	0.84 (0.72–0.96)	0.94 (0.62–1.25)
25 min after	0.82 (0.72–0.91)	0.86 (0.70–1.02)
Umbilical artery PI		
Before extradural block	0.88 (0.75–1.02)	0.86 (0.77–0.95)
5 min after	0.85 (0.75–0.95)	0.88 (0.76–0.99)
10 min after	0.90 (0.79–1.00)	0.87 (0.80–0.94)
20 min after	0.88 (0.81–0.96)	0.80 (0.73–0.87)
25 min after	0.89 (0.80–0.98)	0.83 (0.72–0.93)

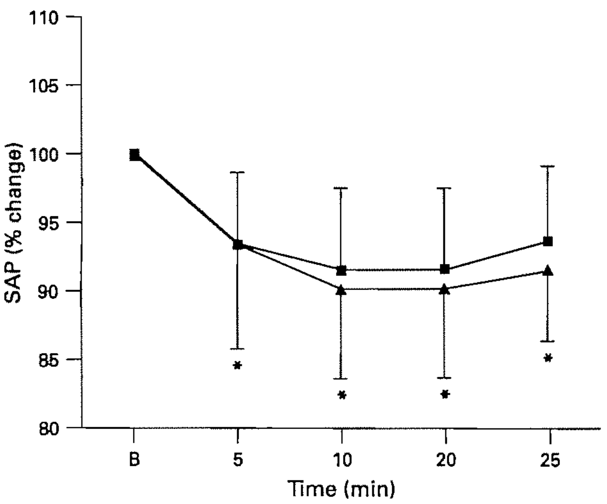

Figure 1 Mean (95 % CI) percentage changes in maternal systolic arterial pressure (SAP) during the study. SAP decreased significantly in both groups after induction of extradural anaesthesia (* $P < 0.05$). B = Before extradural anaesthesia. Time = minutes after the first dose of bupivacaine. There were no significant differences between the single-dose (▲) and fractionated-dose (■) groups.

patient and used for later analysis. Administration of ephedrine and atropine did not result in any significant changes in individual uterine and umbilical artery PI, and therefore all PI values were included in the subsequent analysis. Changes in mean PI values for uterine and umbilical arteries were not significant within or between groups (table 3). One neonate in the fractionated-dose group had an Apgar score of 7 at 1 min. Apgar scores at 5 min were ≥ 8 and pH values in the umbilical artery ≥ 7.17 (range 7.17–7.42) in all neonates in both groups (table 1). Sensory block was adequate for surgery in both groups. One patient in the fractionated-dose group required i.v. opioid (alfentanil) because of visceral pain during surgery. Median level of sensory block was T3 (range T2–5) in the single-dose group and T4 (T3–5) in the other group. This difference, although statistically significant ($P = 0.021$), was clinically irrelevant.

Discussion

Basic mean uterine and umbilical artery PI values observed in this study were in accord with previous findings in uncomplicated late pregnancies [15–18]. We did not measure PI before preloading as earlier studies have shown no difference in PI measured before and after preloading [7, 19, 20]. Under the conditions of this study, a total dose of 23 ml (115 mg) of 0.5 % bupivacaine, given either as a single bolus or in fractionated doses via the extradural catheter, did not have any significant effect on maternal uterine and fetal umbilical artery PI, reflecting only minor changes in vascular resistance in these vessels. Other studies have also shown similar results after administration of 0.5 % plain bupivacaine in fractionated doses [5, 6]. In those two studies, only one ultrasound recording was obtained after induction of extradural block, either when sensory block was at T5 [5] or at 40 min [6]. In this study, Doppler recordings were performed repeatedly four times during establishment of extradural block. We were therefore able to also observe any transient changes in blood flow velocities and indices in these arteries. Giles, Lah and Trudinger [21] performed Doppler ultrasound measurements after preload and again at 15 and 30 min after extradural anaesthesia and observed a decrease in mean uteroplacental and fetal umbilical blood flow resistance in eight healthy parturients. In their opinion, the decrease in flow resistance reflected improved perfusion after maternal plasma volume expansion and extradural block. Patients in that study were examined in a semi-sitting (20°) position, however, which may possibly explain the difference in uteroplacental perfusion, as that position may lead to altered responses in maternal circulation (e.g. venous return) compared with that in the supine position during extradural block.

In contrast, Baumann and colleagues [16] observed an increase in uteroplacental PI after extradural anaesthesia, suggesting impairment of the uteroplacental circulation. In that study, a second ultrasound recording was obtained only once at 15 min after administration of two doses of 0.5% plain bupivacaine (7 ml each) preceded by a 3-ml test dose of 2% lignocaine with adrenaline. The dose of bupivacaine (14 ml) given before Doppler measurement was smaller than usual, and the increased resistance of the uteroplacental circulation was thought to be caused by decreased peripheral vascular resistance resulting in increased blood flow to the legs and subsequently a decrease in uteroplacental perfusion pressure. Alahuhta and colleagues [8] compared the effects of a single injection of 20 ml of 0.5% plain bupivacaine and 0.5% ropivacaine on uteroplacental and fetal circulation and found a significant increase in placental and non-placental uterine artery PI, 5 min after administration of bupivacaine and when sensory block was at T6–T4. In that study, a potential explanation for the increase in uterine artery PI after a bolus dose was a high bupivacaine concentration which caused vasoconstriction in the uterine arteries. In this study, bupivacaine was diluted with saline, however, and so the resulting concentration of local anaesthetic solution was probably lower than that in the former study [8]. The possible difference in concentrations may be one reason why we did not observe such an increase in PI after administration of bupivacaine. Thus it seems that there is variation between the results of several studies with regard to the effects of bupivacaine on vascular resistance in the uterine arteries. It is possible that the varied anaesthetic techniques and timings of Doppler measurements used in other studies [5, 6, 8, 16, 21] may hinder interpretation and comparison of the different results obtained.

Both groups in this study were almost comparable except for difference in weight and the level of sensory block achieved. These differences were clinically insignificant, however, and did not endanger the reliability of the comparison of Doppler measurements between the groups. We found similar changes in maternal heart rate and systolic arterial pressure after administration of bupivacaine with both techniques. Maternal hypotension occurred to a similar extent in both groups and the total incidence of hypotension (23%) observed was comparable with that reported in previous studies using a single bolus dose of bupivacaine [1, 2, 8, 20]. Recently, Griffin and Reynolds [12] reported a high incidence of hypotension after injection of a 20-ml bolus of either 0.5% bupivacaine or 0.5% ropivacaine, that is 83% (29/35) and 76% (28/37), respectively. In that study, however, patients were preloaded with only 500 ml of Hartmann's solution before extradural block, while in studies with preloading volumes of crystalloid solution greater than 1 litre, a lower incidence of hypotension was observed [1, 8, 20]. However, a recent study showed the ineffectiveness of preloading in preventing maternal hypotension caused by spinal anaesthesia for Caesarean delivery [22]. Another possible explanation for the high incidence of hypotension observed by Griffin and Reynolds [12] may be a more rapid onset of sympathetic block after administration of 17 ml of local anaesthetic over 4 min.

In previous studies, maternal and fetal plasma concentrations of bupivacaine measured after administration of a 20-ml bolus were less than toxic concentrations [4, 10, 23, 24] and there was no change in the heart rate pattern of healthy fetuses [10]. An extradural injection of local anaesthetic may still result in toxic maternal and fetal plasma concentrations or total spinal anaesthesia because of accidental intravascular or intrathecal injection. Therefore, local anaesthetics must be given with care in order to avoid these potential and acute life-threatening complications. Neonatal outcome, as assessed by 5-min Apgar scores and umbilical artery pH values, was uneventful in this study and in accord with other studies using a single bolus of local anaesthetic for extradural Caesarean section [1, 8, 10].

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References

1. Laishley RS, Morgan BM. A single dose epidural technique for Caesarean section. A comparison between 0.5% bupivacaine plain and 0.5% bupivacaine with adrenaline. *Anaesthesia* 1988; **43**: 100–103.
2. Laishley RS, Morgan BM, Reynolds F. Effect of adrenaline on extradural anaesthesia and plasma bupivacaine concentrations during Caesarean section. *British Journal of Anaesthesia* 1988; **60**: 180–186.
3. Clark V, McGrady E, Sugden C, Dickson J, McLeod G. Speed of onset of sensory block for elective extradural Caesarean section: choice of agent and temperature of injectate. *British Journal of Anaesthesia* 1994; **72**: 221–223.
4. Price ML, Reynolds F, Morgan BM. Extending epidural blockade for emergency cesarean section. Evaluation of 2% lignocaine with adrenaline. *International Journal of Obstetric Anesthesia* 1991; **1**: 13–18.
5. Alahuhta S, Räsänen J, Jouppila P, Kangas-Saarela T, Hollmén AI. Uteroplacental and fetal haemodynamics during extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1991; **66**: 319–323.
6. Turner GA, Newnham JP, Johnson C, Westmore M. Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms. *British Journal of Anaesthesia* 1991; **67**: 306–309.
7. Long MG, Price M, Spencer JAD. Uteroplacental perfusion after epidural analgesia for elective Caesarean section. *British Journal of Obstetrics and Gynaecology* 1988; **95**: 1081–1082.
8. Alahuhta S, Räsänen J, Jouppila P, Kangas-Saarela T,

Jouppila R, Westerling P, Hollmén AI. The effects of epidural ropivacaine and bupivacaine for cesarean section on uteroplacental and fetal circulation. *Anesthesiology* 1995; **83**: 23–32.

9. Crochetière CT, Trépanier CA, Coté JJ. Epidural anaesthesia for Caesarean section: comparison of two injection techniques. *Canadian Journal of Anaesthesia* 1989; **36**: 133–136.
10. Loftus JR, Holbrook RH, Cohen SE. Fetal heart rate after epidural lidocaine and bupivacaine for elective cesarean section. *Anesthesiology* 1991; **75**: 406–412.
11. Howell P, Davies W, Wrigley M, Tan P, Morgan B. Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *British Journal of Anaesthesia* 1990; **65**: 648–653.
12. Griffin RP, Reynolds F. Extradural anaesthesia for Caesarean section: a double-blind comparison of 0.5% ropivacaine with 0.5% bupivacaine. *British Journal of Anaesthesia* 1995; **74**: 512–516.
13. Ludbrook J. Repeated measurements and multiple comparisons in cardiovascular research. *Cardiovascular Research* 1994; **28**: 303–311.
14. Day SJ, Graham DF. Sample size estimation for comparing two or more treatment groups in clinical trials. *Statistics in Medicine* 1991; **10**: 33–43.
15. Bower S, Vyas S, Campbell S, Nicolaides KH. Color Doppler imaging of the uterine artery in pregnancy: normal ranges of impedance to blood flow, mean velocity and volume of flow. *Ultrasound in Obstetrics and Gynecology* 1992; **2**: 261–265.
16. Baumann H, Alon E, Atanassoff P, Pasch T, Huch A, Huch R. Effect of epidural anesthesia for Cesarean delivery on maternal femoral arterial and venous, uteroplacental, and umbilical blood flow velocities and waveforms. *Obstetrics and Gynecology* 1990; **75**: 194–198.
17. Halpern S, Glanc P, Myhr T, Ryan M, Fong K, Amankwah K, Ohlsson A. Uterine and umbilical blood flow velocity during epidural anaesthesia for Caesarean section. *Canadian Journal of Anaesthesia* 1994; **41**: 1057–1062.
18. Wright PMC, Iftikhar M, Fitzpatrick KT, Moore J, Thompson W. Vasopressor therapy for hypotension during epidural anesthesia for cesarean section: effects on maternal and fetal flow velocity ratios. *Anesthesia and Analgesia* 1992; **75**: 56–63.
19. Morrow RJ, Rolbin SH, Ritchie JWK, Haley S. Epidural anaesthesia and blood flow velocity in mother and fetus. *Canadian Journal of Anaesthesia* 1989; **36**: 519–522.
20. Valli J, Pirhonen J, Aantaa R, Erkkola R, Kanto J. The effects of regional anaesthesia for Caesarean section on maternal and fetal blood flow velocities measured by Doppler ultrasound. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 165–169.
21. Giles WB, Lah FX, Trudinger BJ. The effect of epidural anaesthesia for Caesarean section on maternal uterine and fetal umbilical artery blood flow velocity waveforms. *British Journal of Obstetrics and Gynaecology* 1987; **94**: 55–59.
22. Jackson R, Reid JA, Thorburn, J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 262–265.
23. Fletcher S, Carson R, Reynolds F, Howell P, Morgan B. Plasma total and free concentrations of bupivacaine and lignocaine in mother and fetus following epidural administration, singly or together. *International Journal of Obstetric Anesthesia* 1992; **1**: 135–140.
24. Datta S, Camann W, Bader A, VanderBurgh L. Clinical effects and maternal and fetal plasma concentrations of epidural ropivacaine versus bupivacaine for cesarean section. *Anesthesiology* 1995; **82**: 1346–1352.

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Spinal anaesthesia with 0.25% hyperbaric bupivacaine for Caesarean section: effects of volume

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Summary

To investigate the safety and efficacy of 0.25% hyperbaric bupivacaine for spinal anaesthesia in Caesarean section, we studied 60 parturients allocated randomly to one of three groups. According to the patient's height, groups 1, 2 and 3 received 3.2–3.6 ml (8–9 mg), 3.6–4.0 ml (9–10 mg) and 4.0–4.4 ml (10–11 mg) of 0.25% bupivacaine in 5% glucose, respectively. Subarachnoid injection was performed in the right lateral decubitus position, and parturients were then turned immediately supine with left uterine displacement. Mean spread of sensory analgesia was significantly higher in group 3 (T2–3) than in groups 1 and 2 (T4–5 in each group). Duration of sensory analgesia was significantly longer in groups 2 and 3 than in group 1. Complete motor block of the lower extremities occurred in all patients but in only one in group 1. Onset time and duration of motor block were not significantly different between the three groups. The incidence of hypotension was significantly higher in group 3 (75%) than in groups 1 and 2 (40% in each group). The efficacy of intraoperative analgesia was significantly greater in groups 2 and 3 than in group 1. The incidence of patients requiring analgesics during operation was significantly lower in groups 2 (25%) and 3(10%) than in group 1 (70%). There was no difference in neonatal condition between the three groups. Spinal anaesthesia with 3.6–4.0 ml of 0.25% bupivacaine in 5% glucose was satisfactory for Caesarean section. (*Br. J. Anaesth.* 1996; **77**: 145–149)

Key words

Anaesthetics local, bupivacaine. Anaesthetic techniques, subarachnoid. Anaesthesia, obstetric.

Amylocaine is a drug used frequently for spinal anaesthesia in Caesarean section. However, this agent often fails to provide good maternal sensory block [1, 2]. Recently, bupivacaine has gained popularity in obstetric anaesthesia but 0.5% plain bupivacaine has been shown to be unreliable and produced occasional high block [3, 4]. Therefore, hyperbaric bupivacaine has been used more often than plain bupivacaine for spinal anaesthesia in Caesarean section.

The total dose of bupivacaine is more important than volume or concentration of anaesthetic solution in determining spread of anaesthetic solution in the CSF [5–7]. However, the effect of volume of hyperbaric spinal anaesthetic solution injected may be additive to the effects of gravity, position and dose [8–10]. Almost all parturients given 0.5% hyperbaric bupivacaine 7.5–10 mg for spinal anaesthesia in Caesarean section required supplementary analgesia because of visceral pain during surgery [11, 12]. When hyperbaric bupivacaine 10–15 mg was used for spinal anaesthesia in Caesarean section, good sensory block developed and the incidence of supplementary analgesia was decreased [2, 12]. However, the volume exceeded 3 ml in those cases. When 0.25% hyperbaric bupivacaine solution 10–15 mg is used for spinal anaesthesia in Caesarean section, the volume reaches 4–6 ml, which may influence spinal anaesthesia because of easily cephalad spread of local anaesthetic solution in CSF.

The aim of this investigation was to assess the safety and efficacy of 0.25% bupivacaine in 5% glucose for spinal anaesthesia in Caesarean section. Sensory and motor block, haemodynamic changes, quality of intraoperative analgesia and complications were compared.

Patients and methods

We studied 60 term parturients, ASA I or II, chosen to have spinal anaesthesia for elective Caesarean section. The study was approved by the Hospital Ethics Committee and written informed consent was obtained from all patients at the preoperative visit. Parturients who had obstetric complications or evidence of fetal compromise were excluded. Hyperbaric bupivacaine solution 0.25% was made with the same volume of 0.5% bupivacaine hydrochloride (Marcaine, Astra, Sweden) and 10% glucose monohydrate (Daehan Pharmaceutical Co., Seoul, Korea). The specific gravity of 0.25% bupivacaine in 5% glucose was 1.022 at 23 °C. Patients were allocated randomly to one of three groups. Each group had 10 mothers who were 156–160 cm tall and 10 mothers 161–165 cm tall. Group 1 mothers (156–160 cm tall) were given 3.2 ml of 0.25% bupivacaine in 5% glucose, and those 161–165 cm received 3.6 ml.

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In groups 2 and 3, the corresponding bupivacaine volumes were 3.6 and 4.0 ml, and 4.0 and 4.4 ml, respectively. All subarachnoid blocks were performed by one anaesthetist and data were collected by two registrars who were blinded to the solutions used.

All parturients received ranitidine 10 mg and glycopyrronium 0.2 mg i.m., 1 h before arrival in the operating room. All patients received an infusion of lactated Ringer's solution 1000 ml over 10–20 min before induction. They were also given ephedrine 40 mg i.m., approximately 10 min before subarachnoid injection. Subarachnoid injection was performed in the right lateral decubitus position with a 25-gauge Quincke spinal needle, using a midline approach at the L2–3 or L3–4 interspace. The predetermined volume of local anaesthetic was injected over 20–30 s without barbotage. After subarachnoid injection, mothers were immediately turned supine with left uterine displacement. The parturient's head was rested on a pillow.

The spread of sensory block to pinprick was measured at 2-min intervals during the first 10 min and then at 5-min intervals. The degree of motor block of the lower extremities was also assessed at the same interval, using the modified Bromage scale: 0 = no paralysis; 1 = unable to raise the extended leg; 2 = unable to flex knee; 3 = unable to flex ankle. Maternal arterial pressure and heart rate were recorded every minute until delivery and every 5 min thereafter, using an automated, non-invasive device (Sirecust 404, Simens, Germany). If hypotension (systolic arterial pressure less than 100 mm Hg or a 20% reduction in systolic arterial pressure) occurred, it was treated promptly by increasing uterine displacement and the rate of fluid administration. If hypotension persisted despite these measures, ephedrine 10 mg was given i.v. and repeated as needed. Oxygen was administered routinely by face mask at 6 litre min^{-1} until the end of operation. When sensory block at or above T6 was established, surgery were commenced. The incidence and frequency of complications were noted.

The efficacy of intraoperative analgesia was assessed by the following four categories: excellent = no discomfort during the procedure; good = mild discomfort but required no systemic analgesia; fair = pain that required additional analgesia; and poor = moderate or severe pain that needed more than fentanyl 100 µg or general anaesthesia.

When the patient complained of pain, fentanyl 50 µg was given i.v. and repeated as needed. I.v. midazolam 2.5 mg was administered if the patient requested to sleep after the birth of the baby. I.v. droperidol 0.625 mg was used to treat nausea or vomiting. The times of bupivacaine injection, start of surgery, delivery and termination of surgery were recorded. The condition of the neonates was assessed by Apgar score at 1 and 5 min after delivery. All mothers received oxytocin by continuous infusion after delivery. Return of sensory and motor function was assessed at 15-min intervals until complete recovery from anaesthesia.

All data are expressed as number or mean (SD or range). The results were analysed using one-way and two-way ANOVA followed by Tukey's test for parametric data, and the chi-square test with Yates' correction, the Kruskall-Wallis followed by the Mann–Whitney *U* test for non-parametric data. $P < 0.05$ was considered statistically significant.

Results

There were no statistically significant differences in mean age, weight, height and gestational age between the three groups (table 1). In four patients in group 1, the spinal was converted to general anaesthesia 10–15 min after delivery of the neonate because surgical anaesthesia was inadequate. These patients were excluded from further analysis of sensory and motor block.

Onset and segmental spread of sensory analgesia are shown in figure 1. Cephalad spread of sensory analgesia was increased significantly with an increase in volume, and the differences between groups 1 and 3 and between groups 2 and 3 were significant. Onset time of sensory analgesia to T6 was significantly faster in group 3 than in group 1. The mean maximal level of analgesia in group 3 (T2–3) was significantly higher than that in groups 1 and 2 (T4–5 in each), and the times to achieve the maximal level were similar, with an average of 10–15 min between the three groups. Sensory analgesia at or above T6 was obtained in all patients, but sensory analgesia below

Table 1 Patient characteristics (mean (SD or range))

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Age (yr)	30.0 (23–34)	29.9 (25–35)	29.4 (24–36)
Height (cm)	159.5 (2.4)	158.8 (2.2)	160.6 (2.7)
Weight (kg)	65.0 (8.5)	65.6 (5.9)	68.4 (8.5)
Gestation (weeks)	37.8 (0.9)	38.3 (0.8)	37.9 (2.1)

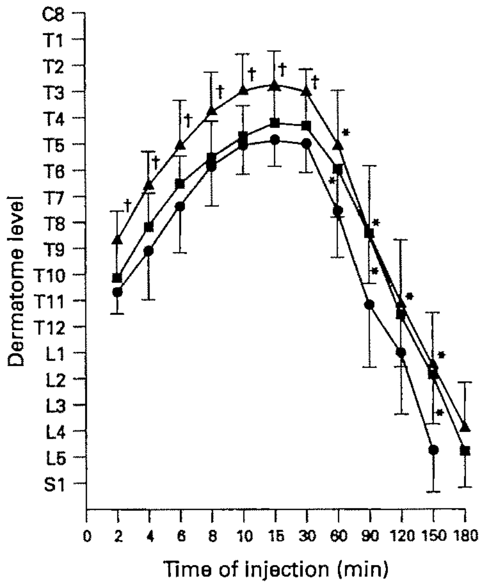

Figure 1 Onset and segmental spread of sensory analgesia after subarachnoid injection of 0.25% bupivacaine in 5% glucose for term parturients in group 1 (3.2–3.6 ml (●)), group 2 (3.6–4.0 ml (■)) and group 3 (4.0–4.4 ml (▲). $^*P < 0.05$ *vs* group 1, $^†P < 0.05$ *vs* groups 1 and 2.

Table 2 Comparison of times of onset and regression of subarachnoid block (mean (SD)). $^*P < 0.05$ *vs* group 1

	Group 1 ($n = 16$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Sensory block (min)			
Time to T6	7.7 (2.4)	6.9 (1.8)	5.5 (2.4)*
Time to maximal level	13.8 (3.2)	12.7 (2.7)	11.9 (3.0)
Regression time to T10	85.0 (15.3)	103.0 (14.3)*	108.5 (20.8)*
Regression time to L5	164.0 (20.3)	185.5 (20.9)*	198.0 (26.8)*
Motor block (min)			
Time to complete block	11.6 (3.7)	12.1 (3.2)	10.7 (3.7)
Time to complete regression	122.0 (25.9)	137.3 (24.5)	142.2 (33.3)

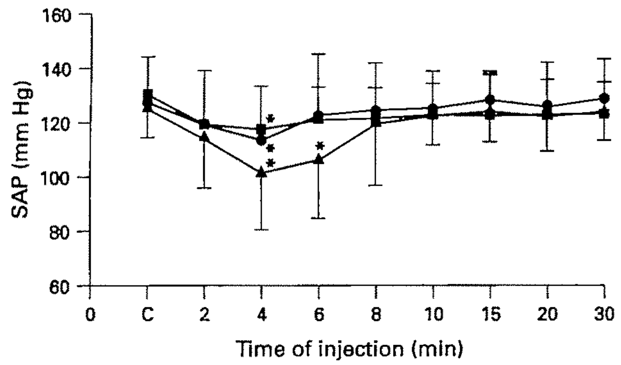

Figure 2 Changes in maternal systolic arterial pressure (SAP) during the first 30 min after subarachnoid injection of 0.25 % bupivacaine in 5 % glucose for term parturients in group 1 (3.2–3.6 ml (●)), group 2 (3.6–4.0 ml (■)) and group 3 (4.0–4.4 ml (▲)). C = Control. $^*P < 0.05$ compared with control value in each group.

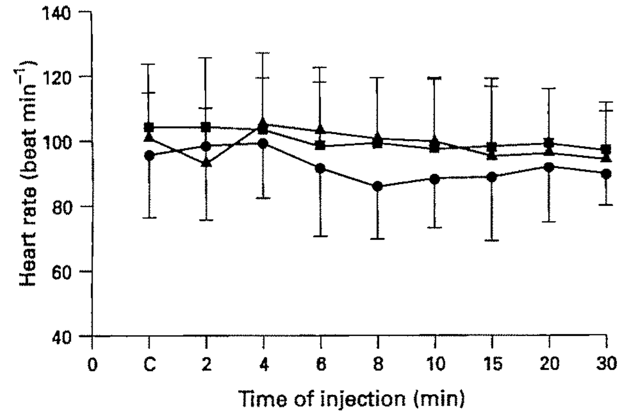

Figure 3 Changes in maternal heart rate during the first 30 min after subarachnoid injection of 0.25 % bupivacaine in 5 % glucose for term parturients in group 1 (3.2–3.6 ml (●)), group 2 (3.6–4.0 ml (■)) and group 3 (4.0–4.4 ml (▲)). C = Control.

Table 3 Incision direction and surgical times (mean (SD) or number). Long/trans = Longitudinal/transverse

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Incision direction			
Long/trans	6/14	7/13	6/14
Induction to operative start time (min)	16.6 (4.5)	16.5 (3.2)	15.9 (3.5)
Induction to operative end time (min)	82.3 (9.3)	84.6 (10.3)	83.2 (8.1)
Uterine incision to delivery time (s)	91.6 (23.2)	78.3 (33.0)	82.5 (26.7)

Table 4 Efficacy of sensory block during surgery (number). $^*P < 0.05$ *vs* group 1

Category	Group 1 ($n = 20$)	Group 2* ($n = 20$)	Group 3* ($n = 20$)
Excellent	4	10	16
Good	2	5	2
Fair	9	5	2
Poor	5	0	0

T4 was obtained significantly more in group 1 (70 %) than in groups 2 and 3 (30 % and 10 %, respectively). Two patients in group 3 had a block up to C6 and C7, respectively. Total time for regression of sensory analgesia to T10 and L5 was significantly longer in groups 2 and 3 than in group 1 (table 2).

Complete motor block of the lower extremities was obtained in all patients at an average time of 10–13 min, except for one patient in group 1 (Bromage scale 2). Duration of complete motor block was longer with an increase in volume, but this was not statistically significant (table 2).

There were no significant differences in systolic arterial pressure and heart rate during the first 30 min between the three groups (figs 2, 3). Compared with control preanaesthetic values, systolic arterial pressure was significantly decreased at 4 min in groups 1 and 2, and at 4 and 6 min in group 3. The percentage maximal decreases in systolic arterial pressure were 16.1 (9.9) %, 17.8 (10.1) % and 25.7 (13.2) % in groups 1, 2 and 3, respectively, recorded 4–6 min after induction of spinal anaesthesia. Hypotension developed in eight of 20 patients in group 1 (40 %), and six required i.v. ephedrine, compared with eight of 20 patients in group 2 (40 %), and seven required i.v. ephedrine and 15 of 20 patients in group 3 (75 %), and 14 required i.v. ephedrine. The incidence of hypotension and need for ephedrine were significantly greater in group 3 than in groups 1 and 2.

The various time intervals from induction of anaesthesia to end of surgery are shown in table 3. There were no significant differences in these times between the groups.

No patient in any group complained of discomfort at incision from skin to the uterus. The efficacy of intraoperative analgesia was significantly greater in groups 2 and 3 than in group 1 (table 4). In group 1, only four patients (20 %) were totally painless; 14 patients (70 %) required supplementary analgesia 40–50 min after induction, four of whom required general anaesthesia about 10–15 min after delivery. Five patients in group 2 (25 %) and two in group 3 (10 %) required supplementary analgesia 50–60 min after induction of spinal anaesthesia.

Neonatal weight and Apgar scores at 1 and 5 min were similar between the three groups (table 5). The condition of the neonates was good. Two infants in group 3 had an Apgar score of 5 and 6, but more than 8 at 5 min.

Table 5 Neonatal status (mean (SD))

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Neonatal weight (kg)	3.3 (0.3)	3.2 (0.2)	3.4 (0.3)
Apgar score			
1 min	8.3 (0.5)	8.4 (0.5)	8.2 (0.8)
5 min	9.5 (0.4)	9.6 (0.3)	9.4 (0.7)

Table 6 Intraoperative complications (number). †Patients in whom droperidol was used. *$P < 0.05$ *vs* groups 1 and 2

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Hypotension	8	8	15*
Bradycardia	4	5	7
Nausea/vomiting†	2	3	6
Dyspnoea	1	2	4
Transient headache	0	0	2

The incidences of complications after spinal anaesthesia are shown in table 6. Complications occurred more in group 3 than in groups 1 and 2, but this was not significant.

Discussion

Our data indicated that 0.25% bupivacaine in 5% glucose could be used safely and effectively for spinal anaesthesia in Caesarean section. Lignocaine, amylocaine and bupivacaine can be used for spinal anaesthesia in Caesarean section but some mothers who received amylocaine spinal anaesthesia needed supplementary analgesia because of intraoperative visceral pain [1, 2]. Recently, bupivacaine has gained popularity in obstetric anaesthesia for extradural and also spinal anaesthesia. Hyperbaric bupivacaine provided better intraoperative analgesia and produced shorter duration of motor block than hyperbaric amylocaine [2].

Within the range of 7.5–12 mg of 0.5% hyperbaric bupivacaine, similar levels of sensory block to T3 occurred, despite the varying doses of drug injected, but the duration of sensory block was longer with the large than the small dose. Increasing the dose increased the intensity of motor block, but the duration of motor block was similar [11, 12]. In our study, increasing the dose increased the level and duration of sensory block, but the intensity and duration of motor block were similar between the three groups.

Several reports [5–7] have suggested that the total dose of bupivacaine is more important than volume or concentration of anaesthetic solution in determining spread of anaesthetic solution in the CSF. The relationship between volume of anaesthetic injected for spinal anaesthesia and final level of block have not been defined clearly. Baricity determines primarily the spread of subarachnoid local anaesthetic in the CSF. In recent studies of plain spinal infusion in pregnancy, final levels of block were similar with volumes and concentrations ranging from 3 ml of 0.5% to 18 ml of 0.083% plain bupivacaine [13–15]. However, increasing the volume administered into the subarachnoid space, especially in a hyperbaric solution, resulted in significantly greater cephalad spread [8–10]. The effect of volume of hyperbaric spinal anaesthetic solution injected may be additive to the effects of gravity, position and dose. High volumes of hyperbaric local anaesthetic solution may influence the spread of local anaesthetic in CSF and final block. In the clinical dose range (10–15 mg) of 0.5% or 0.75% hyperbaric bupivacaine, the volume does not exceed 3 ml. When 0.25% hyperbaric bupivacaine solution is used, the dose of 10–15 mg reaches 3.0–6.0 ml. The large volume itself may influence the spread of local anaesthetic in CSF and final block, especially in the narrow subarachnoid space of term parturients. In our preliminary study with 5–6 ml of 0.25% bupivacaine in 5% glucose, sensory block occurred at the cervical level of dermatome in a few minutes after subarachnoid injection in all parturients. Severe hypotension developed and nausea or vomiting, dyspnoea, and transient headache occurred in all patients.

The one cause limiting the choice of spinal anaesthesia for Caesarean section is the possibility of neonatal depression because of severe hypotension after spinal anaesthesia. Petersen and co-workers [12] reported incidences of hypotension in patients given 7.5–10 mg and 10–12.5 mg of 0.5% hyperbaric bupivacaine solution of 24% and 26%, respectively. In our study, despite adequate hydration and i.m. ephedrine before induction of spinal anaesthesia, the incidence of hypotension in the 4.0–4.4-ml group (75%) was significantly greater than in the 3.2–3.6-ml and 3.6–4.0-ml groups (40% in each group). The percentage maximal decrease in systolic arterial pressure and the incidence of patients requiring supplementary ephedrine were significantly greater in the 4.0–4.4-ml group than in the two other groups. The condition of the neonates, assessed by Apgar score, was good and similar in the three groups. Two neonates in the 4.0–4.4-ml group had an Apgar score of 5 and 6 at 1 min, respectively, but the scores at 5 min were more than 8. In these two neonates, maternal systolic arterial pressure decreased transiently to 70 and 75 mm Hg a few minutes after induction of spinal anaesthesia. A large volume of 0.25% hyperbaric bupivacaine solution could easily spread in a cephalad direction in CSF and influence sensory block and also sympathetic block. Therefore, simply increasing the volume of 0.25% hyperbaric bupivacaine solution to increase the dose must be considered for spinal anaesthesia for Caesarean section.

It is generally accepted that sensory analgesia to at least the fourth thoracic dermatome is necessary for Caesarean section. However, despite seemingly adequate levels of sensory block regardless of the local anaesthetic used, many parturients required supplementary analgesia during exteriorization of the uterus and traction on the abdominal viscera [11, 12]. In our study, all parturients experienced a block at or above T6 in sensory analgesia. Sensory block above T4 was obtained significantly more often in the 3.6–4.0-ml and 4.0–4.4-ml groups than in the 3.2–3.6-ml group. No patient complained of discomfort at incision from skin to the uterus. Petersen and co-workers [12] reported that similar spread of sensory block to above T3 developed in patients who received 7.5–10 mg and 10–12.5 mg of 0.5 % hyperbaric bupivacaine solution, but the use of a larger dose of bupivacaine resulted in a lesser frequency of moderate to severe visceral pain. In our study, the frequency of visceral pain and requirement for supplementary opioids were significantly less in the 3.6–4.0-ml and 4.0–4.4-ml groups than in the 3.2–3.6-ml group.

A variety of ways have been tried to improve the quality of spinal anaesthesia during Caesarean section. Injecting larger doses of local anaesthetic can improve the quality of sensory block [12, 16]. In 0.25 % hyperbaric bupivacaine solution, increasing volume to increase the dose is not recommended because the large volume itself would cause cervical spinal block and severe hypotension. The addition of adrenaline [17], morphine [18] or fentanyl [19] to hyperbaric bupivacaine solution improved the quality of bupivacaine intraoperative analgesia. In our study with 0.25 % hyperbaric bupivacaine, a larger dose improved the quality of sensory analgesia, but the incidence of hypotension and its severity were greater with volumes exceeding 4.0 ml.

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References

1. Schnider SM. Anesthesia for elective cesarean section. In: Schnider SM, ed. *Obstetrical Anesthesia*. Baltimore: Williams and Wilkins, 1970; 94.
2. Michie AR, Freeman, Dutton DA, Howie HB. Subarachnoid anaesthesia for elective Caesarean section. *Anaesthesia* 1988; **43**: 96–99.
3. Russell IF. Spinal anaesthesia for Caesarean section: the use of 0.5 % bupivacaine. *British Journal of Anaesthesia* 1983; **55**: 309–314.
4. Russell IF. Inadvertent total spinal for Caesarean section. *Anaesthesia* 1985; **40**: 199–200.
5. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom H, Covino BG. A dose–response study of bupivacaine for spinal anesthesia. *Anesthesia and Analgesia* 1983; **62**: 931–935.
6. Bengtsson M, Malmqvist L-A, Edstrom HH. Spinal analgesia with glucose-free bupivacaine: effect of volume and concentration. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 583–586.
7. Mukkada TA, Bridenbaugh PO, Singh PM, Edstrom HH. Effects of dose, volume, and concentration of glucose-free bupivacaine in spinal anesthesia. *Regional Anesthesia* 1986; **11**: 98–101.
8. Axelsson KH, Edstrom HH, Sundberg AEA, Widman GB. Spinal anaesthesia with hyperbaric bupivacaine: effects of volume. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 439–454.
9. Chambers WA, Littlewood DG, Edstrom HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administered. *British Journal of Anaesthesia* 1982: 54; 75–80
10. Stienstra R, Greene NM. Factors affecting the subarachnoid spread of local anesthetic solution. *Regional Anesthesia* 1991; **16**: 1–6.
11. Santos S, Pedersen H, Finster M, Edstrom H. Hyperbaric bupivacaine for spinal anesthesia in cesarean section. *Anesthesia and Analgesia* 1984; **63**: 1009–1013.
12. Pedersen H, Santos AC, Steinberg ES, Schapiro HM. Harmon TW, Finster M. Incidence of visceral pain during cesarean section: the effect of varying doses of spinal bupivacaine *Anesthesia and Analgesia* 1989; **69**: 46–49.
13. Van Zundert AA, De Woff AM, Vaes L, Soetens M. High volume spinal anesthesia with bupivacaine 0.125 % for cesarean section. *Anesthesiology* 1988; **69**: 998–1003.
14. Russell IF. Spinal anesthesia for cesarean delivery with dilute solutions of plain bupivacaine: the relationship between infused volume and spread. *Regional Anesthesia* 1991; **16**: 130–136.
15. Vucevic M, Russell IF. Spinal anaesthesia for Caesarean section: 0.125 % plain bupivacaine 12 ml compared with 0.5 % plain bupivacaine 3 ml. *British Journal of Anaesthesia* 1992; **68**: 590–559.
16. DeSimone CA, Norris MC, Leighton B, Epstein R, Palmer C, Kaplan S, Goodman D. Spinal anesthesia with hyperbaric bupivacaine for cesarean section: a comparison of two doses. *Anesthesiology* 1988; **69**: A670.
17. Abouleish EI. Epinephrine improves the quality of spinal hyperbaric bupivacaine for cesarean section. *Anesthesia and Analgesia* 1987; **66**: 395–400.
18. Abouleish E, Rawal N, Fallon K, Hernandez. Combined intrathecal morphine and bupivacaine for cesarean section. *Anesthesia and Analgesia* 1988; **67**: 370–374.
19. Hunt CO, Naulty JS, Bader AB, Hauch MA, Vartikar J, Datta S, Hertwig LM, Ostheimer GW. Perioperative analgesia with subarachnoid fentanyl–bupivacaine for cesarean delivery. *Anesthesiology* 1989; **71**: 535–540.

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Spinal anaesthesia for Caesarean section: effect of Sprotte needle orientation

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Summary

We induced spinal anaesthesia in 100 women presenting for elective Caesarean section with the mother in the right lateral position. Patients were allocated randomly to have the side eye of the 24-gauge Sprotte spinal needle pointing in one of four directions: group A, cephalad; group B, right lateral; group C, left lateral; group D, caudad. Isobaric bupivacaine 0.5% (2.5 ml) was injected over 30 s before the mother was placed supine with a 15° left lateral tilt. Onset time and height of the subsequent analgesic and anaesthetic blocks were assessed by a blinded observer. Onset of sensory block to T4 was significantly faster in group A ($P = 0.001$). There were no differences in final block height, incidence of hypotension, nausea and vomiting or ephedrine requirements. (*Br. J. Anaesth.* 1996; **77**: 150–152)

Key words

Anaesthesia, obstetric. Anaesthetics local, bupivacaine. Anaesthetic techniques, subarachnoid. Equipment, needles.

Spinal anaesthesia for Caesarean section avoids the maternal and fetal risks of general anaesthesia. Side effects associated with spinal anaesthesia include hypotension, nausea and post-dural puncture headache, all of which are more common in the parturient [1].

The incidence of post-spinal headache may be reduced by the use of pencil-point needles which have a lateral eye near the tip of the needle from which local anaesthetic emerges at an angle to the longitudinal line of the needle [2, 3]. This can be manipulated to produce "directional anaesthesia" in which spread of local anaesthetic solution in the cerebrospinal fluid (CSF) is affected by the direction in which the eye of the needle faces [4]. This may be a way of ensuring adequate sensory block for surgery when a single injection spinal technique is used.

Directional spinal anaesthesia using a needle with a side lumen was first described by Kirschner in 1932 [5]. Orientation of the eye of the 22-gauge Whitacre spinal needle has been shown to affect sensory block height in both obstetric [6] and general surgical patients [4]. When the eye of the needle faced caudad rather than cephalad, maximum height of sensory block was lower in general surgical patients [7]. It has been shown that solutions injected through a Whitacre needle exit at a 90° angle to the longitudinal axis of the needle [4]. The Sprotte needle has a larger eye than the Whitacre needle; it is not known if local anaesthetic leaves the Sprotte needle at the same angle as from the Whitacre needle.

The aim of this study was to assess if the direction in which the eye of the Sprotte needle faces during injection of local anaesthetic solution affects the onset of sensory block for Caesarean section and the incidence of side effects.

Patients and methods

We studied 100 women undergoing elective Caesarean section with spinal anaesthesia, at 38–42 weeks' gestation, with a singleton pregnancy. Mothers less than 150 cm or more than 170 cm in height, or with babies displaying evidence of fetal compromise, or with oligo- or polyhydramnios were excluded. The study was approved by the hospital Ethics Committee and all patients gave written informed consent.

Mothers received a preload of crystalloid solution 15 ml kg^{-1} and were then placed in the right lateral position. Spinal anaesthesia was induced with isobaric bupivacaine 2.5 ml via a 24-gauge Sprotte needle at the L2–3 intervertebral space. Patients were allocated randomly to have the lateral eye of the needle facing in one of four directions: a = cephalad, b = right lateral, c = left lateral or d = caudad.

When free flow of cerebrospinal fluid had been confirmed, 0.5% isobaric bupivacaine 2.5 ml was injected over 30 s and the woman placed immediately supine with a 15° left lateral tilt. The subsequent sensory block was assessed using loss of cold

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sensation to ice by one of the authors, who was unaware of the direction of the needle eye; the first assessment was made 3 min after injection of local anaesthetic and then at 2-min intervals until sensory block stopped increasing.

When loss of cold sensation had reached the fourth thoracic dermatomal level, sensory block was assessed with a 25-gauge needle for the anaesthetic level (no sensation to pinprick) and analgesic level (aware of pinprick but does not feel sharp). At this time the extent of sacral block was assessed.

Non-invasive arterial pressure was measured at 2-min intervals. A reduction in systolic pressure to < 70 % of the pre-spinal value or nausea, or both, was treated with ephedrine i.v. Administration of anti-emetics was recorded. Discomfort during Caesarean section was treated with increments of alfentanil 0.25 mg i.v. All mothers were reviewed after operation and their satisfaction with the technique assessed using a 10-cm visual analogue score (VAS).

A power calculation determined that a sample size of 80 women would be required to demonstrate a 2.5-min difference in onset time of sensory block if the SD of onset time was 2.8 min (calculated from an earlier pilot study). This gave the study 80 % power; an additional 20 women were studied in the event that study violations excluded women from analysis. Data were analysed using the Kruskal–Wallis test followed by the Mann–Whitney *U* test and chi-square test as appropriate (statistics package Minitab for windows version 9.2).

Results

Patient data were comparable (table 1).

ONSET OF SENSORY BLOCK

The Kruskal–Wallis test showed a significant difference between groups; onset of sensory block to T4 measured by loss of cold sensation was faster when the eye of the Sprotte needle faced cephalad (group A) ($P = 0.001$). Mann–Whitney comparison showed that group A had a significantly faster onset of sensory block than all other groups (group B, $P = 0.0112$, group C, $P = 0.0035$ and group D, $P = 0.014$). There were no significant differences between groups B, C and D in onset time. Median onset times ranged from 5 min in group A to 8 min in group D (table 2).

Table 2 Time to development of suitable block for surgery (loss of cold sensation). Kruskal–Wallis, $P = 0.001$

	Group			
Onset time to T4 (min)	A	B	C	D
Median (interquartile range)	5.0 (3.0–5.0)	7.0 (5.0–9.0)	6.0 (5.0–8.5)	8.0 (5.0–9.0)

Table 3 Maximum block height (loss of cold sensation) (number of patients at each level). No significant differences (chi-square)

	Group			
	A	B	C	D
< T4	0	0	0	0
T4–T3	8	11	11	14
⩾ T2	16	13	13	10

Table 4 Anaesthetic and analgesic levels to pinprick when loss of cold sensation was at T4 (median (interquartile range)). No significant differences (Kruskal–Wallis)

	A	B	C	D
Anaesthetic block	T6 (7–6)	T7 (8–6)	T7 (7–6)	T7 (8–6)
Min–max block height	T8–T5	T9–T5	T9–T5	T10–T5
Analgesic block	T5 (5–5)	T5 (6–5)	T6 (6–5)	T5 (6–5)
Min–max block height	T6–T4	T7–T4	T7–T4	T8–T4

All women developed adequate sensory block for surgery and there was no difference in final block height achieved between the groups, with maximum block height of T4–C6 (table 3). Although more women in the cephalad group developed sensory block above T1 (four patients compared with one each in both lateral groups and none in the caudad group) this was not significant. None of the women with a high block complained of respiratory symptoms. All mothers had satisfactory sacral block by the time sensory block had reached T4.

The median difference between anaesthetic and analgesic sensory levels, measured immediately before skin incision, was two dermatomes in all groups. Similarly, the median difference between analgesic and loss of cold sensation levels was two dermatomes. The maximum difference between anaesthetic and loss of cold sensation levels was six dermatomes (table 4).

Table 1 Patient data (median (interquartile range))

	Group			
	A	B	C	D
Age (yr)	32 (28–34)	31 (29–35)	30 (25–33.5)	30 (25–35)
Height (cm)	160 (158–163)	161.5 (157.25–165.75)	161 (160–167.25)	163 (157.25–166.75)
Weight (kg)	74 (70–77)	74 (65–80)	74 (69–83)	72 (65.5–83)
Gestation (weeks)	38 (38–39)	38 (38–39)	38 (38–39)	38 (38–39)

Table 5 Operative measures (number of patients)

	Group			
	A ($n = 24$)	B ($n = 24$)	C ($n = 24$)	D ($n = 24$)
Antiemetics	6	5	4	7
Alfentanil	3	5	4	3
Ephedrine	21	15	15	18
VAS for satisfaction (median (IQ))	9.5 (8.7–9.9)	9.5 (8.3–9.9)	9.75 (9.5–10)	9.55 (8.6–9.8)

HYPOTENSION

The incidence of hypotension (a reduction in systolic pressure to < 70 % of pre-spinal value) was high in all groups. There was no significant difference in the number of women requiring ephedrine or in the total dose they received. The incidence of nausea and antiemetic requirements was similar (table 5).

MATERNAL SATISFACTION

Small numbers of women in each group required supplementary analgesia at some time during operation and i.v. alfentanil was given (table 5). Upper levels of sensory block for those who did and did not require alfentanil were comparable. Maternal satisfaction with spinal anaesthesia, assessed by VAS, was high, regardless of Sprotte needle orientation or intraoperative analgesic requirements (table 5).

No woman in the study developed post-dural puncture headache.

Discussion

We found that if the eye of a 24-gauge Sprotte needle faced cephalad during induction of spinal anaesthesia for Caesarean section, onset of sensory block was significantly faster than if it pointed caudad or laterally. Onset of sensory block was slowest when the needle eye faced caudad, although this was not significant. Although the difference in onset time was small (median 5 min in group A and 8 min in group D), it may be important when anaesthesia is required for emergency Caesarean section when a rapid onset of spinal anaesthesia may avoid general anaesthesia with its associated risks.

All women developed adequate sensory block for surgery, regardless of needle orientation. As maximum sensory block height was comparable in all groups, the distributions of local anaesthetic within the CSF were probably similar.

For elective Caesarean section when the onset time of sensory block is less important, orientation of the Sprotte needle is probably irrelevant. However, this contrasts with a previous study in which it was found that spinal injection in the caudad direction failed to provide reliable anaesthesia for Caesarean section; 80 % of women required adjunctive measures (e.g. Trendelenburg position) [6]. The method used in this study was different as a smaller volume (2 ml) of hyperbaric amethocaine (in 10 % glucose) was injected at the L3–4 intervertebral space over a shorter time interval of 15 s. We cannot conclude from our study that anaesthesia would be adequate if spinal injection was made in the sitting position or if hyperbaric bupivacaine was used.

Although onset of sensory block was faster in group A, there was no corresponding increase in the incidence of hypotension or in ephedrine or antiemetic requirements. This contrasts with an earlier study in which it was demonstrated that more ephedrine was required when there was rapid onset of sensory block [8]. More women in the cephalad group had sensory levels (loss of cold sensation) above T1; none had respiratory difficulties.

A total of 15.6 % of women required i.v. alfentanil for discomfort during operation, usually when the peritoneum was handled towards the end of surgery. The maximum dose given was 0.5 mg (incrementally) and requirements were comparable between groups. Satisfaction scores were excellent in all groups. It is unclear why women experience pain during Caesarean section despite apparently adequate regional anaesthesia. It has been suggested that if spinal opioids are not used, an anaesthetic block to T5 is required to prevent pain during Caesarean section under spinal anaesthesia [9]. While the anaesthetic level was below T5 in the majority of women (81 %) at the start of surgery in our study the level probably increased further during surgery, although this was not measured. Our study confirmed that there is an area of differential sensory block at the upper end of a spinal anaesthetic, as described by Russell [9]. In general, anaesthetic levels are two dermatomes lower than analgesic levels, which are two dermatomes lower than loss of cold sensation levels. Confirmation of an adequate anaesthetic level is essential as the maximum difference between anaesthetic and cold sensation levels was six dermatomes when loss of cold sensation was measured at T4 before surgery.

References

1. Kestin IG. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; **66**: 596–607.
2. Hart JR, Whitacre RJ. Pencil point needle in prevention of postspinal headache. *Journal of the American Medical Association* 1951; **147**: 657–658.
3. Cesarini M, Torrielli R, Lahaye F, Mene JM, Cabiro C. Sprotte needle for intrathecal anaesthesia for caesarean section: incidence of postdural puncture headache. *Anaesthesia* 1990; **45**: 656–658.
4. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesthesia and Analgesia* 1985; **64**: 715–730.
5. Kirschner M. Spinal anesthesia placed at will and dosage individually graded. *Surgery, Gynecology and Obstetrics* 1932; **55**: 317.
6. Graham CW, Sutton L, Cozen HJ. Directional spinals in obstetric analgesia. *Anaesthesia* 1978; **33**: 192–195.
7. Neigh JL, Kane PB, Smith CT. Effects of speed and direction of injection on the level and duration of spinal anesthesia. *Anesthesia and Analgesia* 1970; **49**: 912–918.
8. Inglis A, Daniel M, McGrady E. Maternal position during induction of anaesthesia for caesarean section. A comparison of right lateral and sitting positions. *Anaesthesia* 1995; **50**: 363–365.
9. Russell IF. Levels of anesthesia and intraoperative pain at cesarean section under regional block. *International Journal of Obstetric Anesthesia* 1995; **4**: 71–77.

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Soft tissue anatomy within the vertebral canal in pregnant women

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Summary

To clarify pregnancy-induced changes in soft tissue anatomy within the vertebral canal, we have studied magnetic resonance (MR) images of the lumbar spine in three women. In each subject, T2-weighted axial MR images were obtained both before pregnancy and at 32 weeks' gestation, and the paired images were compared. The extradural venous plexus was engorged significantly in supine parturients. In addition, the engorged extradural venous plexus displaced the dura away from the wall of the vertebral canal in a posterior direction, which resulted in a decrease in the volume of the cerebrospinal fluid in the dural sac. These findings confirmed the long-held concept that the engorged extradural venous plexus in supine parturients decreases the effective capacity of the extradural and subarachnoid spaces. (*Br. J. Anaesth.* 1996; **77**: 153–156)

Key words

Anatomy, extradural space. Anaesthesia, obstetric. Pregnancy. Measurement techniques, magnetic resonance imaging.

Obstruction of the inferior vena cava by the enlarged pregnant uterus impairs the return of venous blood from the legs and pelvis to the heart [1, 2]. The collateral circulation includes the intraosseous vertebral veins, paravertebral veins and extradural venous plexus. Of these, the engorged extradural venous plexus is expected to decrease the effective capacity of the extradural and subarachnoid spaces [3–5], and parturients may require less anaesthetic agent for induction of extradural or spinal anaesthesia.

Although the engorged extradural venous plexus during pregnancy has been demonstrated well by radiological studies of the inferior vena cava [1, 2, 5], few objective data are available to confirm the decrease in the capacity of the extradural and subarachnoid spaces. Magnetic resonance (MR) imaging provides detailed information on soft tissue anatomy within the vertebral canal [6, 7]. To clarify pregnancy-induced changes in soft tissue anatomy within the vertebral canal, we performed MR imaging both before and during pregnancy in volunteers.

Subjects and methods

The Institutional Review Board approved our study and informed consent was obtained from three women aged 28, 30 and 31 yr. MR imaging examinations were performed twice in each subject: before pregnancy (non-pregnant) and at 32 weeks' gestation (pregnancy). All MR images were obtained with the subject supine and with the legs extended. T2-weighted axial MR images of the second and third lumbar vertebrae were obtained using an MR imaging system (MRT-200/FXIII super version, Toshiba Corporation, Tokyo, Japan) operating at 1.5 T with a single surface coil. Technical specifications included a repetition time of 3000 ms, echo time of 112 ms, slice thickness of 4 mm, number of slices of 9 and a field of view of 15 cm. On each slice level, we compared the paired images (non-pregnant *vs* pregnancy) with each other in the same subject. Measurements obtained from MR images included the following: maximum distance between the anterior surface of the ligamentum flavum and the dura; area of the fat-filled posterior extradural space at the level of the intervertebral disc between the second and third lumbar vertebrae; and area of the dual sac at the level of the intervertebral disc between the second and third lumbar vertebrae. The areas were measured using a digital planimeter (KP-90N, Uchida Yoko, Ltd, Tokyo, Japan).

Results

ANATOMY IN NON-PREGNANT STATE

The extradural space around the dura varied in shape and size depending on the longitudinal site of the axial slices. At the level of the intervertebral disc, the anterior extradural space was absent as the annular ligament of the disc was in direct contact wtih the dural sac (fig. 1A). The fat-filled posterior extradural space which was enclosed by the ligamentum flavum, the articular capsule and the dura was present posteriorly. The fat in this space, appearing as a triangle, had a high signal and was uniform (white). The lateral and posterior extradural spaces were discontinuous, separated by areas of contact of the dura with the ligamentum flavum. At the level of the pedicles, virtually no contents were identified in the extradural space except veins anteriorly (fig. 2A). At the level of the lamina, the extradural space, which contained nerve roots, vessels and fat, opened up lateral to the dura (fig. 3A).

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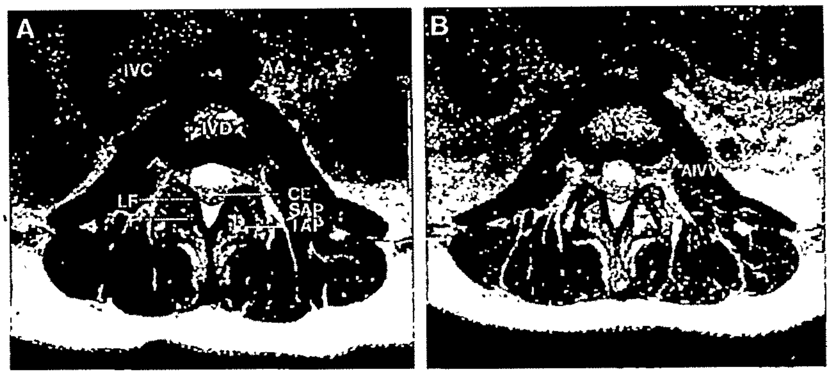

Figure 1 T2-weighted MR images showing an axial section through the L2–3 intervertebral disc before pregnancy (A) and at 32 weeks' gestation (B). AA = Abdominal aorta, IVC = inferior vena cava, IVD = intervertebral disc, CE = cauda equina, SAP = superior articular process, IAP = inferior articular process, LF = ligamentum flavum, F = posteromedial extradural fat, AIVV = anterior internal vertebral vein. The anterior extradural space is absent as the annular ligament of the disc is in direct contact with the dural sac. During pregnancy, the anterior vertebral veins are engorged, particularly on both sides of the extradural space. The fat-filled posterior extradural space which is enclosed by the ligamentum flavum, the articular capsule and the dura remains unchanged during pregnancy. The fat in this space, appearing as a triangle, has a high signal and is uniform (white).

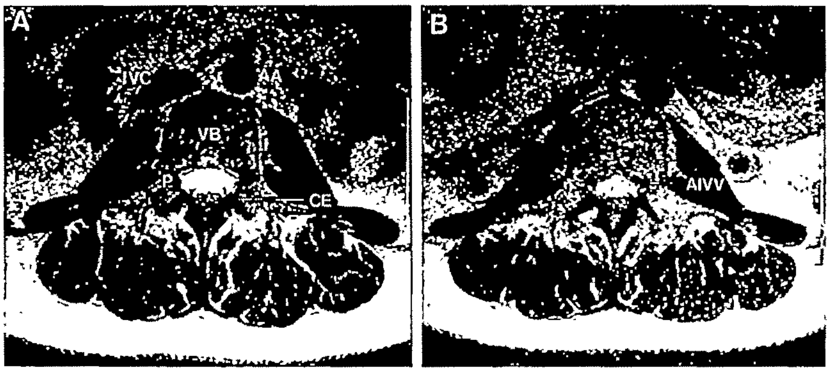

Figure 2 T2-weighted MR images showing an axial section at the level of the pedicles of L3 before pregnancy (A) and at 32 weeks' gestation (B). AA = Abdominal aorta, IVC = inferior vena cava, VB = vertebral body, P = pedicle, CE = cauda equina, AIVV = anterior internal vertebral vein. Virtually no contents are identified in the extradural space except veins anteriorly before pregnancy (A). The anterior vertebral veins are substantially engorged during pregnancy (B).

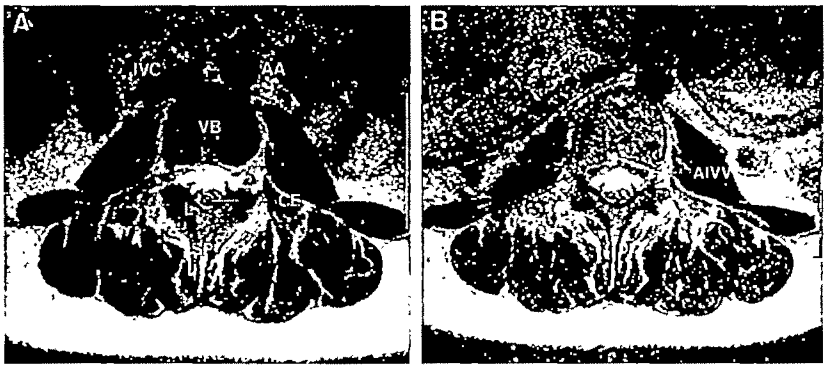

Figure 3 T2-weighted MR images showing an axial section at the level of the lamina of L3 before pregnancy (A) and at 32 weeks' gestation (B). AA = Abdominal aorta, IVC = inferior vena cava, VB = vertebral body, L = lamina, SP = spinous process, CE = cauda equina, AIVV = anterior internal vertebral vein. The engorged anterior internal vertebral veins displace the dura away from the wall of the vertebral canal in a posterior direction (B).

CHANGES IN ANATOMY DURING PREGNANCY

With the parturient supine, the enlarged pregnant uterus pressed down the abdominal aorta and inferior vena cava against the vertebral body. In particular, the inferior vena cava was almost totally obstructed (figs 1B, 2B and 3B). The extradural venous plexus was substantially engorged. The engorgement was noted in the anterior vertebral veins (figs 1B, 2B and 3B). The engorged anterior vertebral veins displaced

Table 1 Body weight and measurements in the three women before pregnancy (non-pregnant) and at 32 weeks' gestation (pregnancy)

	Non-pregnant	Pregnancy
Weight (kg)		
Patient No. 1	53	60
Patient No. 2	37	47
Patient No. 3	45	51
Ligamentum flavum–dura mater (mm)		
Patient No. 1	8	8
Patient No. 2	5	5
Patient No. 3	6	6
Area of the posterior extradural space at L2–3 (cm^2)		
Patient No. 1	0.5	0.5
Patient No. 2	0.3	0.3
Patient No. 3	0.3	0.3
Area of the dural sac at L2–3 (cm^2)		
Patient No. 1	1.8	1.5
Patient No. 2	2.1	1.8
Patient No. 3	1.3	1.1

the dura away from the wall of the vertebral canal in a posterior direction (figs 2B and 3B), which resulted in a decrease in the volume of cerebrospinal fluid in the dural sac. The fat-filled posterior extradural space remained unchanged during pregnancy (fig. 1B). Measurements obtained are documented in table 1.

Discussion

Injection of a given dose of local anaesthetics into the extradural space or subarachnoid space produces more extensive segmental block in late pregnancy than at other times [3–5, 8]. Possible explanations for this increased sensitivity to regional anaesthesia include anatomical and hormonal changes associated with pregnancy [9–14].

The dural sac is enclosed completely by the rigid vertebral canal and tissues of the central nervous system are incompressible. Because the volume of the intradural contents remains unchanged, the volumes of blood and CSF within the vertebral canal must vary in inverse relationship to each other [5]. In the later stages of pregnancy the gravid uterus compresses both the inferior vena cava and abdominal aorta, whenever the gravida lies in the supine position [1, 2, 15]. Obstruction of the inferior vena cava diverts a proportion of the venous return from the legs and pelvic structure into the vertebral venous system, which is composed of three freely communicating valveless networks: intraosseous vertebral veins, paravertebral veins and the extradural venous plexus [16]. Of these, the engorged extradural venous plexus is expected to decrease the effective capacity of the extradural [3] and subarachnoid spaces [4, 5]. These decreased spaces are considered to be one of the reasons for pregnancy-induced enhancement of regional anaesthesia.

Examination of the soft tissue anatomy within the vertebral canal has been performed by radiographic methods such as extradurography [17], extradural venography [16, 18], myelography [5] and computed tomography [19]. Because these radiographic examinations include fetal hazards for exposure to x-rays, changes in soft tissue anatomy during pregnancy have not been investigated fully, although they are traditionally considered to influence significantly the spread of regional anaesthesia in parturients. In contrast with radiographic examinations, MR imaging, without the use of x-rays, provides detailed information on soft tissue anatomy within the vertebral canal [6, 7]. The signal intensity of circulating blood is extremely low on T2-weighted MR images, and hence not only large vessels but also small vessels can be identified without the use of contrast media. The intensity of CSF in the adjacent dural sac appears slightly higher than that of extradural fat. Thus T2-weighted MR images provided quantitative data on the effective capacity of the extradural and subarachnoid spaces.

The extradural venous plexus was engorged significantly in our supine parturients. In addition, the engorged extradural venous plexus displaced the dura away from the wall of the vertebral canal in a posterior direction, which resulted in a decrease in the volume of cerebrospinal fluid in the dural sac. These findings confirm the long-held concept that the engorged extradural venous plexus in supine parturients decreases the effective capacity of the extradural and subarachnoid spaces [3–5], and parturients may therefore require less anaesthetic agent for induction of extradural or spinal anaesthesia.

A surprising finding was that the fat-filled posterior extradural space remained unchanged during pregnancy, although the anterior and lateral extradural space significantly altered its feature. The extradural venous plexus is composed of two vertical channels, the anterior vertebral veins that course the length of the vertebral canal, hugging the backs of the vertebral bodies and intervertebral discs [16]. The anterior vertebral veins, consisting of medial and lateral components, lie medial to the pedicles and bulge laterally as they cross the intervertebral disc spaces. The findings observed in the MR images of our parturients were consistent with engorgement of the anterior vertebral veins. On the other hand, there is increasing evidence to indicate that the posterior vertebral veins are rudimentary or do not exist [16, 18, 20, 21], although anatomy texts always describe such a system [22–27]. Indeed, a review of 1200 lumbar extradural venograms demonstrated that the posterior vertebral veins were not seen during venography [16]. Failure of the posterior extradural space to alter during pregnancy probably confirms the absence of a system of posterior vertebral veins.

The number of subjects examined in this study was small. Within-subject comparison, however, made it possible to demonstrate clearly the pregnancy-induced changes in soft tissue anatomy within the vertebral canal in the later stages of pregnancy. In addition, we have demonstrated occlusion of the inferior vena cava in the supine position at 32 weeks' gestation. This supports the recommendation that pregnant women, especially during the later stages of pregnancy, should never be allowed to adopt the supine position, although our parturients did not complain of any discomfort during the examination.

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References

1. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. *British Medical Journal* 1964; **1**: 532–533.
2. Scott DB. Inferior vena caval occlusion in late pregnancy and its importance in anaesthesia. *British Journal of Anaesthesia* 1968; **40**: 120–128.
3. Bromage PR. *Epidural Analgesia*. Philadelphia: WB Saunders, 1978; 141.
4. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesthesia and Analgesia* 1985; **64**: 715–730.
5. Barclay DL, Renegar OJ, Nelson EW. The influence of inferior vena cava compression on the level of spinal anesthesia. *American Journal of Obstetrics and Gynecology* 1968; **101**: 792–800.
6. Westbrook JL, Renowden SA, Carrie LES. Study of the anatomy of the extradural region using magnetic resonance imaging. *British Journal of Anaesthesia* 1993; **71**: 495–498.
7. Grenier N, Kressel HY, Schiebler ML, Grossman RI, Dalinka MK. Normal and degenerative posterior spinal structures: MR imaging. *Radiology* 1987; **165**: 517–525.
8. Bonica JJ. Maternal anatomic and physiologic alternations during pregnancy and parturition. In: Bonica JJ, McDonald JS, eds. *Principles and Practice of Obstetric Analgesia and Anesthesia*, 2nd Edn. Baltimore: Williams & Wilkins, 1995; 45–82.
9. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Furuse M. Anatomical configuration of the spinal column in the supine position. II. Comparison of pregnant and non-pregnant women. *British Journal of Anaesthesia* 1995; **75**: 6–8.
10. Flanagan HL, Datta S, Lambert DH, Gissen AJ, Covino B. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesthesia and Analgesia* 1987; **66**: 123–126.
11. Datta S, Lambert DH, Gregus J, Gissen A, Covino BC. Differential sensitivities of mammalian nerve fibers during pregnancy. *Anesthesia and Analgesia* 1983; **62**: 1070–1072.
12. Datta S, Hurley RJ, Naulty JS, Stern P, Lambert DH, Concepcion M, Tulchinsky D, Weiss JB, Ostheimer GW. Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women. *Anesthesia and Analgesia* 1986; **65**: 950–954.
13. Butterworth JF, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology* 1990; **72**: 962–965.
14. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Cerebrospinal fluid progesterone in pregnant women. *British Journal of Anaesthesia* 1995; **75**: 683–687.
15. Bieniarz J, Crottogini JJ, Curuchet E, Romeo-Salinas G, Yoshida T, Poseiro JJ, Caldeyro-Barcia R. Aortocaval compression by the uterus in late human pregnancy. II. An arteriographic study. *American Journal of Obstetrics and Gynecology* 1968; **100**: 203–217.
16. Gershater R, St Louis EL. Lumbar epidural venography: Review of 1200 cases. *Neuroradiology* 1979; **131**: 409–421.
17. Luyendijik W. The plica mediana dorsalis of the dura mater and its relation to lumbar peridurography (canalography). *Neuroradiology* 1976; **11**: 147–149.
18. Gershater R, Holgate RC. Lumbar epidural venography in the diagnosis of disc herniations. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine* 1976; **126**: 992–1002.
19. Haughton VM, Syvertsen A, Williams AL. Soft-tissue anatomy within the spinal canal as seen on computed tomography. *Neuroradiology* 1980; **134**: 649–655.
20. Theron J, Houtteville JP, Ammerich H, de Souza AA, Adam H, Thurel CL, Rey A, Houdart R. Lumbar phlebography by catheterization of the lateral sacral and ascending lumbar veins with abdominal compression. *Neuroradiology* 1976; **11**: 175–182.
21. Renard M, Larde D, Masson JP, Roland J. Anatomical and radioanatomical study of the lumbo-sacral intervertebral venous plexuses. *Anatomica Clinica* 1980; **2**: 21–28.
22. Platzer W. *Pernkopf Anatomy, vol. II. Thorax, Abdomen and Extremities*, 3rd Edn. Baltimore-Munich: Urban and Schwarzenberg, 1989; 305.
23. Leonhardt HvH, Krisch B, Kubik S, Lange W, Leonhardt H, Leuenbergen P, Töndury G, Zilles K. Band III. Nervensystem, Sinnesorgane. In: Leonhardt HvH, Tillmann B, Töndury G, Zilles K, eds. *Anatomie des Menschen, Lehrbuch und Atlas*. Stuttgart: Georg Thieme Verlag, 1987; 110.
24. Williams PL, Warwick R, Dyson M, Bannister LH. *Gray's Anatomy*, 37th Edn. Edinburgh: Churchill Livingstone, 1989; 811.
25. Clemente CD. *Anatomy, A Regional Atlas of the Human Body*, 3rd Edn. Baltimore-Munich: Urban and Schwarzenberg, 1987; figs 571–573.
26. Agur AMR. *Grant's Atlas of Anatomy*. Baltimore: Williams and Wilkins, 1991; 229.
27. Woodburne RT, Burkel W. *Essential of Human Anatomy*, 8th Edn. Oxford: Oxford University Press, 1988; 340.

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Thrombelastography changes in pre-eclampsia and eclampsia

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D. G. KENOYER AND S. BYRNE

Summary

We have measured platelet count, bleeding time and thrombelastography (TEG) variables and the correlation between these variables in 49 pregnant patients presenting with pre-eclampsia or eclampsia. Eighteen patients (37%) had a platelet count $\leqslant 150 \times 10^9$ litre^{-1} and seven (14%) had a platelet count $\leqslant 100 \times 10^9$ litre^{-1}. Bleeding time was prolonged > 9.5 min in 13 (27%) patients and the TEG was abnormal in four (8%). The TEG variables, k time and maximum amplitude (MA) had a strong correlation with platelet count (k time–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = -0.68$, $P = 0.003$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = -0.84$, $P = 0.02$; MA–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = 0.72$, $P = 0.001$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = 0.78$, $P = 0.04$). There was no correlation between bleeding time and thrombocytopenia (platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = -0.18$, ns; platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = 0.09$, ns). There was no correlation between bleeding time and any measured TEG variable. Of the 10 (20%) patients with an adequate platelet count ($> 100 \times 10^9$ litre^{-1}) but prolonged bleeding time, the TEG was normal, suggesting adequate haemostasis. An MA of 53 mm, which is the lower limit for normal pregnancy, correlated with a platelet count of 54×10^9 litre^{-1} (95% confidence limits 40–75×10^9 litre^{-1}). Although the number of patients with severe thrombocytopenia was small, a platelet count of 75×10^9 litre^{-1} should be associated with adequate haemostasis. (*Br. J. Anaesth.* 1996; **77**: 157–161)

Key words

Blood, coagulation. Measurement techniques, thrombelastography. Anaesthetic techniques, regional. Complications, pre-eclampsia.

Normal pregnancy is associated with an increased incidence of thrombocytopenia, with 6.6% of pregnant women presenting with platelet counts less than 150×10^9 litre^{-1} [1]. In addition, pre-eclampsia may complicate up to 12% of pregnancies and is often associated with abnormalities of haemostasis [2]. Although thrombocytopenia may occur in up to 50% of patients with severe disease [3], clotting factors are rarely affected [4]. Platelet dysfunction may also be present as tests of platelet aggregation [5] and bleeding times may be abnormal [6], despite adequate platelet numbers. Parturients also frequently require extradural anaesthesia and despite the ready availability of platelet counts and coagulation tests, the lower limit of platelet count at which safe regional anaesthesia can be performed is unclear. In addition, the relevance of platelet dysfunction and the usefulness of the bleeding time are uncertain. Thus there is a need for a specific, sensitive and rapid bedside test of haemostasis [7].

The thrombelastograph (TEG) is an on-site monitor that measures all phases of coagulation to clot retraction [8]. Its usefulness, compared with standard laboratory tests of coagulation, has been described during liver transplantation [9] and after cardiopulmonary bypass [10]. TEG changes in normal pregnancy and labour [11–13], and in pre-eclampsia [14, 15] have been reported.

The aim of this study was first, to assess if the TEG could be used to detect haemostatic abnormalities in patients with pre-eclampsia or eclampsia, as demonstrated by abnormal platelet counts and standard laboratory tests of coagulation; second, to determine if a correlation existed between any TEG variable and platelet count to determine a platelet count at which TEG variables become abnormal, thus enabling some guidelines for a lower limit of platelet count at which regional anaesthesia should be avoided; and third, to use the TEG to assess overall haemostasis in a group of patients with normal platelet counts but prolonged bleeding times.

Patients and methods

Approval for the study was obtained from the Professional and Ethics Standards Sub-Committee of the Faculty of Medicine, University of Natal. Informed consent was obtained from all patients, except those with eclampsia. Patients presenting to the delivery suite with a diagnosis of pre-eclampsia

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or eclampsia were entered into the study. Mild pre-eclampsia was defined as a systolic pressure > 140 mm Hg, diastolic > 90 mm Hg and proteinuria > 0.3 g litre^{-1} (1 or 2+ using dipstick measurement). Severe pre-eclampsia was diagnosed by one or more of the following criteria: systolic pressure > 160 mm Hg, diastolic pressure > 110 mm Hg or proteinuria > 5 g litre^{-1} (3 or 4+). The diagnosis of eclampsia was based on a documented history of a recent convulsion in any patient presenting with other features of pre-eclampsia without any previous history of epilepsy and in whom no other cause for convulsions could be determined. Patients with a history of bleeding disorders or recent ingestion of antiplatelet medication within the previous week were excluded.

After admission, arterial pressure was recorded and i.v. infusion of crystalloid started. Blood was sampled through a 19-gauge steel Butterfly needle using a three-syringe technique. The first sample was discarded, the second used for laboratory tests and the third sample used for TEG measurement. This last sample was obtained in a polypropylene syringe and transferred immediately to a polypropylene tube from which 0.36 ml of whole blood was pipetted into the prewarmed cuvette of a thrombelastograph (Thrombelastograph D, Helige, Freiburg in Breisgau). The TEG was situated in the delivery suite facilitating rapid commencement of measurement and was performed in a standard manner.

Bleeding time was measured using a modified Ivy technique with a disposable Simplate II (Organon, Durham) device on the lateral aspect of the volar surface of the forearm. Before incision a sphygmomanometer cuff was inflated to 40 mm Hg and blotting paper was used every 30 s to remove the blood without touching the edges of the incision. All bleeding time tests were performed by the same person (C.E.P.O.) and the TEG result was not available until completion of the bleeding time.

The following laboratory tests were obtained: haematology (haemoglobin, platelet count and mean platelet volume (mpv)), biochemistry (urea, creatinine, calcium, magnesium, albumin and uric acid), coagulation tests (prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and clotting factors (fibrinogen, antithrombin III, protein C, factors V and VIII, and fibrin degradation products). Platelet counts were measured by automatic Coulter Counter.

Patients were studied as soon as possible after admission to the obstetric unit and choice of prophylaxis against or pharmacological control of convulsions and management of hypertension was the decision of the attending obstetrician.

Data were analysed using Pearson's correlation coefficients. Spearman's correlation was used if the groups were small ($n < 10$). Non-linear regression models were fitted to describe relationships between variables where appropriate. Patients were also evaluated further according to their platelet count: $\leqslant 150 \times 10^9$ litre^{-1} or $\leqslant 100 \times 10^9$ litre^{-1}. Values are expressed as mean (SD) and $P < 0.05$ was considered significant.

Results

We studied 49 patients over a 3-month period. The study group comprised seven patients with mild pre-eclampsia, 33 with severe pre-eclampsia and nine with eclampsia. Of the 49 patients, 18 (37%) had a platelet count $\leqslant 150 \times 10^9$ litre^{-1} and seven of these (14% of total) $\leqslant 100 \times 10^9$ litre^{-1}. Tests of coagulation (prolonged PT and reduced fibrinogen) were outside the normal range in two patients. In both of these patients, platelet count was less than 100×10^9 litre^{-1} and the TEG was abnormal. The TEG was abnormal in another two patients (total 8%), with MA reduced in all four. Three of these patients presented with the lowest platelet counts in the series (30, 36 and 59×10^9 litre^{-1}). The fourth patient had a platelet count of 286×10^9 litre^{-1}, normal PT, APTT and fibrinogen, normal bleeding time but mpv was 7.4 fl (normal range 7.4–10.4 fl). The patient with a platelet count of 30×10^9 litre^{-1} and reduced MA (43 mm) also had prolonged *r* (10.5 min) and *k* (6.0 min) times but normal PT, APTT and fibrinogen. In addition to the reduced MA, *k* time (5.5 min) was prolonged in another patient with a prolonged PT (13 s). Laboratory data, TEG variables and bleeding times are shown in table 1 and the number of patients with abnormal results according to platelet count are shown in table 2.

Table 1 Haematology and clotting results, TEG variables and bleeding times for all pre-eclamptic and eclamptic patients, and normal pregnancy values. Results are mean (SD). No significant differences between the two groups

Variable	Normal pregnancy	Term pre-eclampsia–eclampsia
Haematology		
Haemoglobin (g dl^{-1})	> 10	10.9 (1.5)
Platelet count ($\times 10^9$ litre^{-1})	> 150	199 (90)
Mean platelet volume (fl)	7.4–10.4	9.7 (1.5)
Coagulation tests		
PT (s)	10.2 (0.6)	10.4 (0.9)
APTT (s)	28.5 (3.1)	24.9 (3.6)
Fibrinogen (g dl^{-1})	5.3 (1.0)	5.4 (1.4)
Fibrin degradation products (ng ml^{-1})	< 200	327 (682)
Factor V (%)	109 (15)	105 (36)
Factor VIII (%)	204 (46)	245 (129)
ATIII (%)	98 (10)	83 (15)
Protein C (%)	85 (12)	89 (29)
Template bleeding time		
Bleeding time (min)	2.5–9.5	8.5 (4.7)
TEG		
r time (min)	7.8 (0.9)	6.8 (1.0)
k time (min)	3.3 (0.7)	3.1 (0.8)
MA (mm)	59.7 (3.5)	61.7 (6.6)

Table 2 Number of patients according to platelet count ($\times 10^9$ litre^{-1}) with corresponding abnormalities in TEG and bleeding time (BT). *This patient did not have an abnormal bleeding time

	No.	MA < 53 mm	BT > 9.5 min
Platelets < 50	2	2	1
Platelets 50–100	5	1	2
Platelets 100–150	11	0	5
Platelets > 150	31	1*	5

Table 3 Correlation coefficients (P value) between platelet count (PC), fibrinogen, fibrin degradation products (XDP) and TEG variables (k time and MA).

	k (min)	MA (mm)
Platelet count		
All patients ($n = 49$)	−0.37 (0.009)	0.35 (0.01)
PC $\leqslant 150 \times 10^9$ litre ($n = 18$)	−0.68 (0.003)	0.72 (0.001)
PC $\leqslant 100 \times 10^9$ litre^{-1} ($n = 7$)	−0.84 (0.02)	0.78 (0.04)
Fibrinogen		
All patients ($n = 49$)	−0.35 (0.02)	0.50 (0.0003)
PC $\leqslant 150 \times 10^9$ litre^{-1} ($n = 18$)	−0.60 (0.01)	0.72 (0.001)
PC $\leqslant 100 \times 10^9$ litre^{-1} ($n = 7$)	−0.69 (0.08)	0.86 (0.01)
XDP		
All patients ($n = 49$)	0.54 (0.0001)	−0.52 (0.0001)
PC $\leqslant 150 \times 10^9$ litre^{-1} ($n = 18$)	0.57 (0.02)	−0.67 (0.003)

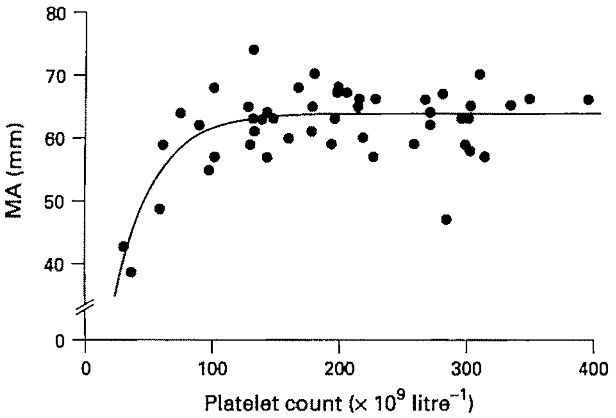

Figure 1 Scattergram of maximum amplitude (MA) of the thrombelastograph *vs* platelet count. The equation MA = 63.9 × (1 − exp (−0.033 platelets)) represents a negative exponential curve of best fit which has been calculated using a non-linear regression procedure.

Drug therapy (number of cases) at the time of evaluation included methyldopa (30), dihydralazine (22), nifedipine (8), diazepam (7), phenobarbitone (22), magnesium (10) and dexamethasone (8).

Correlation coefficients between platelet counts, fibrinogen and fibrin degradation products, and TEG variables, k time and MA, are shown in table 3; none of the above correlated with r time. There was no significant correlation between any TEG variable and PT, APTT, TT, factors V and VIII, antithrombin III, protein C, and serum concentration of urea, creatinine, calcium, magnesium and albumin.

There was a strong correlation between the TEG variables, k time and MA, and platelet count (k time–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = -0.68$, $P = 0.003$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = -0.84$, $P = 0.02$; MA–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = 0.72$, $P = 0.001$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = 0.78$, $P = 0.04$). Figure 1 shows a "hockey stick" relationship between MA and platelet count for all 49 patients. However, this relationship was linear for those seven patients with a platelet count $\leqslant 100 \times 10^9$ litre^{-1}. An MA of 53 mm, which is our lower limit for normal pregnancy (table 1), correlated with a platelet count of 54×10^9 litre^{-1} (95% confidence limits $40–75 \times 10^9$ litre^{-1}) (fig. 1). For all patients, there was a weak but significant negative correlation between bleeding time and platelet count ($r = -0.41$, $P = 0.003$), but no significant correlation in those patients with a platelet count $\leqslant 150 \times 10^9$ litre^{-1} or those with a platelet count $\leqslant 100 \times 10^9$ litre^{-1} ($r = -0.18$ and 0.09 respectively) (fig. 2). Bleeding time was prolonged in 13 (27%) patients. In those with a platelet count $> 100 \times 10^9$ litre^{-1}, 10 (20%) patients had prolonged bleeding times despite a normal TEG. There was no correlation between bleeding time and any TEG variable (r time $= -0.18$, k time $= 0.24$, MA $= -0.26$).

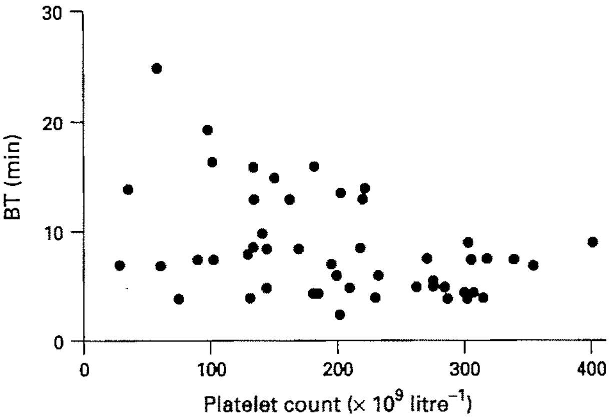

Figure 2 Scattergram of bleeding time (BT) *vs* platelet count. There was only a weak ($r = 0.41$, $P = 0.003$) correlation between the two variables.

Discussion

Platelet counts less than 150×10^9 litre^{-1} have been reported in 6.6% and less than 100×10^9 litre^{-1} in 1.2% of pregnant women in a study of more than 15000 deliveries [1]. The major causes were incidental thrombocytopenia of pregnancy (74%) and hypertensive diseases of pregnancy (21%). Severity of pre-eclampsia is an important determinant of the effect on platelets, with thrombocytopenia in up to 50% with severe disease [3]. Because coagulation factors are rarely reduced and only in the presence of thrombocytopenia, platelet count is a good screening test, with tests of coagulation reserved for those with reduced platelets [4]. These tests are generally available in most hospitals, but in practice time taken for these results to be available can vary enormously. However, the lower limit of platelet count at which regional anaesthesia can be performed safely is not clear, the importance of platelet dysfunction in pre-eclampsia is uncertain and the clinical relevance of bleeding time has been questioned [16]. Thus a machine that assesses haemostasis easily and rapidly in the delivery suite might not only be useful as a screening device but also may provide further information on overall clot formation in patients with reduced platelet counts or those at risk from platelet dysfunction.

The TEG is useful as it is compact, easily located within the delivery suite, relatively easy to use and produces initial results within 30 min.

The TEG measures whole blood clotting and the interaction between the protein coagulation cascade, fibrinogen and the platelet surface, from initiation of clotting to the final stages of clot lysis or retraction [8]. Thus the TEG has been found to be particularly useful during liver transplantation [9] and after cardiopulmonary bypass [10].

In normal pregnancy, reports of changes in the TEG are similar to normal values and are consistent with the hypercoagulable changes in pregnancy [12]. TEG changes of hypocoagulability have been described in a group of patients with severe pre-eclampsia, reduced platelet count and increased aspartate aminotransferase (AST) concentrations [14]. The TEG was used to diagnose and subsequently treat two episodes of haemorrhage in a patient with HELLP syndrome where conventional tests of coagulation were unhelpful [17]. Its use in three non-obstetric patients, with potential haemostatic abnormalities before regional anaesthesia, has also been described [18]. The TEG was used to assist risk of bleeding in a patient with idiopathic thrombocytopenic purpura with a reduced platelet count who underwent uneventful extradural anaesthesia [19].

In our small series, the TEG performed satisfactorily as a screening test compared with platelet count and laboratory tests of coagulation (PT, APTT and fibrinogen). MA was reduced in four patients. Three of these had the lowest platelet counts of the series. In the fourth patient, although platelet count appeared adequate, mean platelet volume (mpv) was 7.4 fl (normal pregnancy 7.4–10.4 fl). As mpv is increased in patients with pre-eclampsia [20], mpv was low for this patient. Platelet aggregation to ADP, collagen or adrenaline is directly proportional to platelet volume [21] and in thrombocytopenic patients, reduced mpv has been shown to be associated with an increased incidence of bleeding episodes [22]. As the TEG has been shown to correlate with platelet aggregation after cardiopulmonary bypass [23], the reduced MA is best explained by platelet dysfunction associated with smaller platelets.

Abnormalities of coagulation were rare in our study and in keeping with the findings of others that prolongation of the PT and APTT is seen only in those in whom platelet count is less than 100×10^9 litre^{-1} [4]. In our series, PT was slightly prolonged in two patients and associated with an abnormal TEG. TEG variables reflect the interdependence of platelets and clotting factors because the TEG is determined in whole blood, unlike laboratory tests which measure isolated aspects of coagulation in plasma. This is clearly illustrated in one patient with a platelet count of 30×10^9 litre^{-1} and reduced MA. Both r and k times were prolonged but PT and APTT were normal. Platelet phospholipid is necessary for the activation of factor X and prothrombin, and in the presence of a very low platelet count, the clotting cascade is affected, resulting in prolonged r and k times. In contrast, as phospholipid substitute is added during laboratory measurements, PT and APTT were normal. Our findings of a correlation between fibrin degradation products and MA and k are consistent with the documented inhibitory effects of fibrin degradation products on the conversion of fibrinogen to fibrin [24].

The 37 % incidence of thrombocytopenia (platelet count $< 150 \times 10^9$ litre^{-1}) in our patients with severe pre-eclampsia/eclampsia is similar to other studies: 34 % in a group of patients with severe disease [25] and 20 % in a group with both mild and severe disease [6]. Unfortunately, there are no clear guidelines in the literature on the safe level of platelet count at which extradural anaesthesia can be performed safely. In this study, none of the patients with a platelet count less than 100×10^9 litre^{-1}, a prolonged bleeding time or an abnormal TEG received a regional anaesthetic.

Anaesthetists are reluctant to perform an extradural block in patients with platelet counts less than 100×10^9 litre^{-1} [26], although a limit of 80×10^9 litre^{-1} has been suggested [27]. Our overall finding of a low correlation between TEG variables and platelet count has been reported previously in pregnant [12] and non-pregnant subjects [28]. This finding is not surprising as the TEG, by measuring overall clot strength, would be expected to remain relatively constant over a wide normal range of platelets. However, it is only when platelet numbers start to decrease to below a critical level that any linear relationship between TEG variables (k and MA) and platelet count is seen. Although the number of patients with a platelet count $< 100 \times 10^9$ litre^{-1} in our series was small, we have calculated that a platelet count of 54×10^9 litre^{-1} is associated with adequate TEG derived clot formation (95 % confidence limits $40–75 \times 10^9$ litre^{-1}). As the upper limit of our 95 % confidence interval for this relationship is a platelet count of 75×10^9 litre^{-1}, we conclude that patients with pre-eclampsia with platelet counts greater than this should not have regional anaesthesia denied to them. In another series of patients with severe pre-eclampsia, TEG was normal in three patients with a platelet count of $50–100 \times 10^9$ litre^{-1} [14]. Thus there is increasing evidence that regional anaesthesia is not contraindicated in patients with platelet counts as low as 75×10^9 litre^{-1}. At this time and because we do not have sufficient data, we cannot recommend that the TEG be used in isolation from an automated platelet count in deciding whether or not to use regional anaesthesia in a patient with severe pre-eclampsia. However, this is unlikely to happen because of the ready availability of automated platelet count machines. As more units obtain TEG machines we shall be able to assess more adequately the value of the TEG in conjunction with platelet count.

Bleeding time has been described to test for adequacy of haemostasis in those with reduced platelets [27, 29]. We found this test particularly unhelpful. One patient with a platelet count of 30×10^9 litre^{-1}, reduced fibrinogen, prolonged PT and abnormal TEG had a bleeding time of only 4 min. We were unable to demonstrate any correlation between platelets and bleeding time in those with a platelet count $< 100 \times 10^9$ litre^{-1}, in contrast with a study by Ramanathan and colleagues who reported a correlation of -0.76 in this group [6].

Platelet function is altered in pre-eclampsia and *in vitro* platelet aggregation may be reduced despite the presence of a normal platelet count [5]. Bleeding time has been used to test for this platelet defect and has been found to be prolonged in 34% of patients with severe pre-eclampsia and a platelet count > 100×10^9 litre^{-1} [6] and in 25% with a platelet count > 150×10^9 litre^{-1} [25]. In our patients with severe pre-eclampsia, 20% had a prolonged bleeding time in the presence of a platelet count > 100×10^9 litre^{-1}, yet the TEG was normal. The TEG is sensitive to qualitative abnormalities of platelets and a significant positive correlation between MA and platelet aggregation and collagen and adenosine diphosphate after cardiopulmonary bypass has been demonstrated [23]. Based on our findings, excluding these patients for regional anaesthesia is inappropriate.

Because *in vivo*, clotting occurs on cell surfaces rather than in plasma, the TEG performed on whole blood may provide a better indicator of the dynamics of clot formation than standard laboratory tests of coagulation which are measured in plasma. However, *in vivo*, haemostasis begins with platelet adhesion to the damaged vessel wall, and the TEG cannot measure this initial interaction between platelets and vascular endothelium. As a result, if the platelet defect is caused by interference with the normal interaction between platelets and vascular endothelium, then the TEG is unable to detect this effect, as occurs in uraemic patients or patients receiving aspirin [30]. Pre-eclampsia is associated with endothelial damage, impaired production of prostacycline and increased deposition of fibrin within the vascular bed. The TEG does not measure these local changes, but can be used to determine the effects on overall clotting associated with reduced platelet counts.

References

1. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *New England Journal of Medicine* 1993; **329**: 1463–1466.
2. Pritchard JA, Macdonald PC. In: Macdonald PC, ed. *Williams Obstetrics*, 16th Edn. New York: Appleton Century Crofts, 1980; 551.
3. Burrows RF, Hunter DJF, Andrew M, Kelton JG. A prospective study investigating the mechanism of thrombocytopenia in preeclampsia. *Obstetrics and Gynecology* 1987; **70**: 334–338.
4. Leduc L, Wheeler JM, Kirshon B, Mitchell P, Cotton DB. Coagulation profile in severe preeclampsia. *Obstetrics and Gynecology* 1992; **79**: 14–18.
5. Whigham KAE, Howie PW, Drummond AH, Prentice CRM. Abnormal platelet function in pre-eclampsia. *British Journal of Obstetrics and Gynaecology* 1978; **85**: 28–32.
6. Ramanathan J, Sibai BM, Vu T, Chauhan D. Correlation between bleeding times and platelet counts in women with preeclampsia undergoing cesarean section. *Anesthesiology* 1989; **71**: 188–191.
7. Cross MH, Haxby EJ, Robinson PN, Bleeding time. *Lancet* 1991; **338**: 187.
8. Mallett SV, Cox DJA. Thrombelastography. *British Journal of Anaesthesia* 1992; **69**: 307–313.
9. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW, Starzl TE, Winter PM. Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. *Anesthesia and Analgesia* 1985; **64**: 888–896.
10. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Comparison of viscoelastic measurements of coagulation after cardiopulmonary bypass. *Anesthesia and Analgesia* 1989; **69**: 69–75.
11. Wall MH, Chadwick HS, Chandler W, Ross BK. Thromboelastography in healthy laboring women and in women receiving magnesium for premature labor. *Anesthesiology* 1993; **79**: A993.
12. Sharma S, Wallace D, Sidawi E, Lacour T, Yamanouchi K, Padakandla B. Thromboelastography with disposable cups and pins: normal measurements in non-pregnant, pregnant and post-partum women. *Anesthesia and Analgesia* 1995; **80**: S432.
13. Steer PL, Kranz HB. Thromboelastography and sonoclot analysis in the healthy parturient. *Journal of Clinical Anesthesia* 1993; **5**: 419–424.
14. Chadwick HS, Wall MH, Chandler W, Ross BK. Thromboelastography in mild and severe preeclampsia. *Anesthesiology* 1993; **79**: A992.
15. Sharma S, Wallace D, Sidawi E, Whitten C, Davenport M, Gambling D. Thromboelastography: assessment of coagulation abnormalities in preeclamptic patients. *Anesthesia and Analgesia* 1995; **80**: S433.
16. Rodgers RPC, Levin J. A critical reappraisal of the bleeding time. *Seminars in Thrombosis and Hemostasis* 1990; **16**: 1–20.
17. Whitta RKS, Cox DJA, Mallett SV. Thrombelastography reveals two causes of haemorrhage in HELLP syndrome. *British Journal of Anaesthesia* 1995; **74**: 464–468.
18. Bigeleisen PE, Kang Y. Thrombelastography as an aid to regional anaesthesia: preliminary communication. *Regional Anaesthesia* 1991; **16**: 59–61.
19. Steer PL. Anaesthetic management of a parturient with thrombocytopenia using thrombelastography and sonoclot analysis. *Canadian Journal of Anaesthesia* 1993; **40**: 84–85.
20. Stubbs TM, Lazarchick J, Van Dorsten P, Cox J, Loadholt CB. Evidence of accelerated platelet production and consumption in nonthrombocytopenic preeclampsia. *American Journal of Obstetrics and Gynecology* 1986; **155**: 263–265.
21. Karpatkin S. Heterogeneity of human platelets. VI. Correlation of platelet function with platelet volume. *Blood* 1978; **51**: 307–316.
22. Eldor A, Avitzour M, Or R, Hanna R, Penchas S. Prediction of haemorrhagic diathesis in thrombocytopenia by mean platelet volume. *British Medical Journal* 1982; **285**: 397–400.
23. Tuman KJ, McCarthy RJ, Patel RV, Ivankovich AD. Comparison of thromboelastography and platelet aggregometry. *Anesthesiology* 1991; **75**: A432.
24. Letsky EA. Disseminated intravascular coagulation. In Morgan B, ed. *Problems in Obstetric Anesthesia.* New York: John Wiley and Sons Ltd, 1987; 69–87.
25. Kelton JG, Hunter DJS, Neame PB. A platelet function defect in preeclampsia. *Obstetrics and Gynecology* 1985; **65**: 107–109.
26. Gutsche BB, Cheek TG. Anesthetic considerations in preeclampsia–eclampsia. In: Shnider SM, Levinson G, eds. *Anesthesia for Obstetrics.* Baltimore: Williams and Wilkins, 1993; 305–336.
27. Letsky EA. Haemostasis and epidural anaesthesia. *International Journal of Obstetric Anaesthesia* 1991; **1**: 51–54.
28. Zuckerman L, Cohen E, Vagher JP, Woodward E, Carprini JA. Comparison of thrombelastography with common coagulation tests. *Thrombosis and Haemostasis* 1981; **46**: 752–756.
29. Douglas MJ. Coagulation abnormalities and obstetric anaesthesia. *Canadian Journal of Anaesthesia* 1991; **38**: R17–21.
30. Mallett SV, Cox DJA. Thrombelastography—assessment of coagulation status and haemostatic therapy. *Care of the Critically Ill* 1993; **9**: 99–102.

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Alfentanil-mediated analgesia during propofol injection: no evidence for a peripheral action

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Summary

We have investigated if alfentanil acts via peripheral opioid receptors to relieve the pain which occurs on injection of propofol. Thirty seconds before induction of anaesthesia and immediately after a tourniquet at 50 mm Hg greater than systolic pressure was inflated on the upper arm, patients were given either placebo ($n = 22$), alfentanil 1 mg ($n = 22$) or lignocaine 40 mg ($n = 22$) via an i.v. cannula in the dorsum of the hand. Pain during injection of propofol was assessed using a three-point verbal rating scale, recorded at 8-s intervals. We found a significant reduction in pain after lignocaine compared with the two other groups ($P < 0.001$), but there was no difference between the placebo and alfentanil groups. We conclude that alfentanil does not relieve pain on injection with propofol via an action on peripheral opioid receptors when alfentanil is limited to the forearm for 30 s before induction of anaesthesia. (*Br. J. Anaesth.* 1996; **77**: 162–164)

Key words

Anaesthetics i.v., propofol. Analgesics opioid, alfentanil. Receptors, opioid. Pain, injection.

Recent work suggests that opioid analgesia may be mediated, at least in part, via peripheral opioid receptors [1]. Prior administration of alfentanil is known to reduce the pain that occurs after an injection of propofol [2]. In a recent study alfentanil was given 15 s before propofol [3]. Significant analgesia was demonstrated approximately 30 s after administration of alfentanil. This rapid onset of analgesic effect is inconsistent with other pharmacodynamic data [2, 4] for alfentanil. This may be explained by alfentanil acting, at least partially, on peripheral opioid receptors. In this double-blind, placebo-controlled study, we have further investigated this phenomenon by pretreatment with alfentanil in the presence of a tourniquet. We also compared the efficacy of alfentanil with lignocaine, an agent which acts locally to prevent propofol-induced pain [5].

Patients and methods

After obtaining Ethics Committee approval and informed consent, we studied 66 patients. Patients were ASA I–II, aged 18–65 yr, undergoing elective day-case surgery and were unpremedicated. After transfer to the anaesthetic room, non-invasive monitoring was commenced and a 22-gauge i.v. cannula sited in the dorsum of the non-dominant hand. Patients were allocated randomly using a sealed envelope technique to one of three groups ($n = 22$ in each group): group 1 received normal saline, group 2 alfentanil 1 mg and group 3 lignocaine 40 mg. A tourniquet was applied to the non-dominant arm, the cuff inflated to 50 mm Hg greater than systolic arterial pressure and the pretreatment dose injected in a total volume of 2 ml. All solutions were prepared by the same investigator (I.W.) who did not assess pain. Thirty seconds after the pretreatment bolus, the tourniquet was deflated and propofol 10 mg ml^{-1} was infused at a rate of 1200 ml h^{-1} using a Graseby 3400 infusion pump. Patients were then asked by a blinded second investigator (K.G.), to assess any discomfort in the arm below the level of the tourniquet at 8-s intervals using a three-point verbal rating scale (none, mild, severe) until loss of consciousness. The time taken to induce anaesthesia, and the volume of propofol required, were noted.

Statistical analysis was by ANOVA and chi-square, as appropriate, with $P < 0.05$ as significant. Previous work has indicated that alfentanil reduces the pain of injection of propofol by at least 50% [2]. On this basis 22 patients were needed in each group to confer a power of 0.9 at a P value of 0.05.

Results

The three groups were similar in age, weight and sex distribution, with no significant differences for duration of induction of anaesthesia. The dose of propofol given was significantly smaller in those who received alfentanil than in the two other groups (table 1).

Pain reported by patients in the three groups is shown in table 2. When considering the worst pain for each patient throughout the study, there was significantly less pain reported by patients who were given lignocaine before propofol compared with the two other groups ($P < 0.001$) (table 3). There was no difference in pain between patients who received alfentanil and placebo (table 3).

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Table 1 Patient data, volume of propofol given and time taken to induce anaesthesia (mean (SD or range) or number). The only significant difference between groups was the volume of propofol used in the alfentanil group (*$P < 0.05$)

	Saline group	Alfentanil group	Lignocaine group
Age (yr)	34.18 (17–55)	33.95 (18–52)	33.36 (23–46)
Sex (M:F)	1:19	1:19	2:18
Weight (kg)	61.53 (12.9)	65.60 (8.7)	64.10 (9.7)
Propofol (ml)	18.70 (2.2)	16.52 (2.3)*	18.90 (3.1)
Induction time (s)	50.10 (6.2)	45.68 (6.0)	50.90 (10.2)

Table 2 Number of patients who were asleep or reporting none, mild or severe pain at 8-s intervals during induction of anaesthesia with propofol. Each column shows the distribution of the 22 patients at each time

	Time (s)							
	8	16	24	32	40	48	56	64
Saline ($n = 22$)								
Asleep	0	0	0	0	2	11	20	22
None	13	8	7	8	8	6	1	0
Mild	7	8	8	7	7	1	0	0
Severe	2	6	7	7	5	4	1	0
Alfentanil ($n = 22$)								
Asleep	0	0	0	0	7	15	22	22
None	11	11	11	12	8	5	0	0
Mild	4	5	8	7	6	2	0	0
Severe	5	6	3	3	1	0	0	0
Lignocaine ($n = 22$)								
Asleep	0	0	0	0	4	9	18	22
None	22	22	21	21	16	11	3	0
Mild	0	0	1	1	2	2	1	0
Severe	0	0	0	0	0	0	0	0

Table 3 Worst pain reported by patients in each group after injection of propofol. Patients in the lignocaine group reported less pain than the two other groups ($P < 0.001$)

	Saline group ($n = 22$)	Alfentanil group ($n = 22$)	Lignocaine group ($n = 22$)
None	7	11	20
Mild	7	4	2
Severe	8	7	0

Discussion

The use of propofol for induction of anaesthesia is common and has been shown to be associated with pain in up to 84% of patients [3]. Many different factors have been associated with this phenomenon, including the temperature of the solution [6], size of the vein and speed of injection [7]. It has been shown that both lignocaine and alfentanil are effective in reducing the discomfort caused by propofol [2, 5] and that lignocaine has its maximum effect when given as pretreatment with a venous tourniquet occluding the proximal part of the arm [8].

Fletcher, Seavell and Bowen gave a bolus of alfentanil 15 s before induction of anaesthesia with propofol and showed a reduction in pain from 84% to 36% [3]. This difference started to become apparent 31 s after alfentanil has been given. This rapid onset of action conflicts with the published pharmacodynamic data of a half-time for access of alfentanil to the central biophase of 54 s [4] and a peak onset time of 90–120 s [2]. We designed this study to see if this discrepancy might be explained in part by alfentanil acting via peripheral opioid receptors to relieve the pain on injection of propofol. Peripheral opioid receptors have been identified in both animals and humans [9, 10]. Their physiological function is unclear, although it has been suggested that they may play a role in the inflammatory response [1] and recent work has suggested that both morphine and pethidine may relieve pain via peripheral opioid receptors when injected into the knee after arthroscopy [11].

In this study we were careful to control for cannula size and the temperature and rate of infusion of propofol. We included a group pretreated with lignocaine and a placebo group as we wished to compare the effects of an agent which is known to act locally, with any peripheral effect of alfentanil.

The incidence of pain in our saline and lignocaine groups supports the findings of a previous study where a venous tourniquet was used [8]. The combination of a tourniquet with lignocaine renders this a highly effective method for relieving the pain of injection of propofol, as Mangar and Holak demonstrated in their work. In our study, two patients in the lignocaine group complained of mild pain in the upper arm at 40 s (table 2) and it may be that to totally prevent pain it is necessary to use a larger volume of injection.

The statistically significant finding of reduced dose of propofol in the alfentanil group compared with those who received saline and lignocaine was not unexpected as Wall and Zacharias demonstrated a similar finding in their study [2]. Although not statistically significant, seven patients being asleep at 40 s in the alfentanil group compared with four in the lignocaine group and two in the saline group at the same time, makes our results more difficult to interpret, however, there are several interesting observations. The worst pain reported by patients receiving alfentanil confined to the forearm using an arterial tourniquet was comparable with those who received saline. This contrasts with the finding that alfentanil used without a tourniquet does relieve propofol pain [2, 3], suggesting that alfentanil acts solely at central opioid receptors. Examining our results more closely (table 2), there may be a reduction in the incidence of pain in the alfentanil compared with the saline group from 24 s onwards, as there were four fewer patients with severe pain (four more with no pain) at both 24 and 32 s. However, if this was the result of a peripheral opioid effect, we would have expected to also detect a difference between groups at earlier times having already pretreated the forearm with alfentanil for 30 s.

There are no data to indicate the time for alfentanil to access a potential peripheral biophase. We accept that 30 s may be too short a time for alfentanil to achieve this. However, if a peripheral opioid action contributed to the analgesia observed by Fletcher, Seavell and Bowen at 30 s, we anticipated reproducing the effect by confining alfentanil to the arm for this time before injection of propofol. Increasing tourniquet time results in greater discomfort in the patient's arm and ethical considerations limited us to this time period for our initial study. However, the rapid onset time of alfentanil found by Fletcher, Seavell and Bowen is inconsistent with known pharmacodynamic data, as stated above. One explanation could be that when given as a rapid bolus the half-time for access to the central biophase is actually less than 54 s, and with a relatively mild pain stimulus, lower concentrations of alfentanil are required at receptors to provide adequate analgesia. It is also possible that we have used an inappropriate opioid and further studies might examine the use of more potent or lipid soluble opioids.

References

1. Stein C. Peripheral mechanisms of opioid analgesia. *Anesthesia and Analgesia* 1993; **76**: 182–191.
2. Wall RJ, Zacharias M. Effects of alfentanil on induction and recovery from propofol anaesthesia in day surgery. *Anaesthesia and Intensive Care* 1990; **18**: 214–218.
3. Fletcher JE, Seavell CR, Bowen DJ. Pretreatment with alfentanil reduces pain caused by propofol. *British Journal of Anaesthesia* 1996; **74**: 342–344.
4. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *Journal of Pharmacological and Experimental Therapeutics* 1987; **240**: 159–166.
5. Johnson RA, Harper NJN, Chadwick S, Vohra A. Pain on injection of propofol. *Anaesthesia* 1990; **45**: 439–442.
6. McKirrick, Hunter S. Pain on injection of propofol: the effect of injectate temperature. *Anaesthesia* 1990; **45**: 443–444.
7. Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–494.
8. Mangar D, Holak EJ. Tourniquet at 50 mmHg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. *Anesthesia and Analgesia* 1992; **74**: 250–252.
9. Stein C, Hassan AHS, Przewlocki R, Gramsch C, Peter K, Herz A. Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proceedings of the National Academy of Sciences USA* 1990; **87**: 5935–5939.
10. Lawrence AJ, Joshi GP, Michalkiewicz A, Blunnie WP, Moriarty DC. Evidence for analgesia mediated by peripheral opioid receptors in inflamed synovial tissue. *European Journal of Clinical Pharmacology* 1992; **43**: 351–355.
11. Lyons B, Lohan D, Flynn CG, Joshi GP, O'Brien TM, McCaroll M. Intra-articular analgesia for arthroscopic menisectomy. *British Journal of Anaesthesia* 1995; **75**: 552–555

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Psychophysical and electrophysiological responses to experimental pain may be influenced by sedation: comparison of the effects of a hypnotic (propofol) and an analgesic (alfentanil)

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Summary

Sedation may influence the responses of some experimental pain models used to test analgesic efficacy. In this study we compared the effects of a sedative (propofol) and analgesic (alfentanil) on: nociceptive reflex to single and repeated electrical stimulations; mechanical pressure pain; and evoked potentials elicited by nociceptive (electrical and laser) and non-nociceptive (acoustical) stimulation. We studied 12 healthy volunteers with two subanaesthetic concentrations of propofol and two analgesic concentrations of alfentanil. Both propofol and alfentanil increased the threshold for nociceptive reflex to single electrical stimulations, but only alfentanil increased the threshold for nociceptive reflex to repeated electrical stimulations. The pressure pain tolerance thresholds were increased significantly by alfentanil, whereas propofol significantly decreased the thresholds (hyperalgesia). Propofol and alfentanil induced similar reductions in the amplitudes of the evoked potentials elicited by nociceptive (electrical and laser) and non-nociceptive (acoustical) stimulation, whereas only alfentanil reduced the perceived pain to nociceptive stimulations. We have shown that sedation can influence both the psychophysical and electrophysiological responses of some experimental pain tests used to measure analgesic efficacy, and that propofol in subhypnotic doses, has no analgesic effect on painful electrical and heat stimulations, but has a hyperalgesic effect on mechanical pressure pain. (*Br. J. Anaesth.* 1996; **77**: 165–171)

Key words

Anaesthetics i.v., propofol. Analgesics opioid, alfentanil. Pain, experimental.

Testing the sensory aspects of pain is hampered by the subjective and multidimensional nature of pain. This has led to a search for quantitative measures. The nociceptive withdrawal reflex to single electrical stimulations of the sural nerve has been proposed as a technique to assess the excitability of the nociceptive system [1, 2]. The size of the evoked potential elicited by painful stimuli has also been found to correlate with the state of the nociceptive system [3, 4]. For conditions when the subject cannot collaborate, nociceptive reflex and evoked potentials would appear to be adequate tests. Spinal polysynaptic nociceptive reflexes have been used in animals for decades. In a recent study [5], we found that subanaesthetic (0.10–0.26 vol% end-tidal) isoflurane concentrations increased significantly the threshold for nociceptive reflex to single electrical stimulations of the sural nerve, but did not change the reaction to pain elicited by heat, cold or pressure, or the threshold for nociceptive reflex to repetitive stimuli. This indicates that the increase in the threshold of the nociceptive reflex to single electrical stimuli might not reflect analgesia but could be caused by sedation. Furthermore, in another study [6] using similar subanaesthetic isoflurane concentrations, we found that the amplitude of evoked vertex potentials elicited by nociceptive laser and intracutaneous electrical stimulations decreased with increasing isoflurane concentration. But isoflurane caused a similar decrease in amplitudes of evoked vertex potentials elicited by non-nociceptive auditory stimuli, indicating that the decrease in amplitude was not caused by an analgesic effect of isoflurane, but could be a result of general depression of neuronal transmission.

Therefore, it seems possible that sedation could influence the responses of some experimental pain models used to assess analgesic efficacy. In this study we compared the effects of sedation (propofol) and analgesia (alfentanil) on the thresholds of the nociceptive reflex to single and repeated electrical stimulations, the amplitude of evoked vertex potentials elicited by nociceptive and non-nociceptive stimuli and detection and tolerance thresholds to mechanically induced pain.

Several studies [7–12] have been designed to see if hypnotics are hyperalgesic in subhypnotic doses, but results are conflicting. As propofol is one of the most widely used hypnotics in anaesthesia, and is also

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used for sedation in intensive care, it is important to clarify further its influence on nociception in humans.

Subjects and methods

We studied 12 healthy volunteers (eight male), mean age 26 (range 20–42) yr. They were not receiving any medication, had no allergies or earlier adverse reactions to anaesthesia, and for the female volunteers, were not pregnant. Written informed consent according to the Helsinki Declaration was obtained, and the study was approved by the Ethics Committee of the Faculty of Medicine, University of Bern.

To minimize the risk of acid aspiration, volunteers were tested after a fasting period of at least 6 h. During testing volunteers rested comfortably in the supine position. An i.v. infusion of NaCl-glucose was started and haemoglobin oxygen saturation by pulse oximetry, ECG and non-invasive arterial pressure were monitored continuously during the study.

NOCICEPTIVE REFLEX THRESHOLD TO SINGLE STIMULI

The sural nerve was stimulated behind the lateral malleolus via surface electrodes filled with electrode gel (inter-electrode distance approximately 2 cm). A 25-ms, train-of-five, 1-ms, square-wave impulse (perceived as a single stimulus) was delivered from a computer-controlled constant current stimulator (University of Aalborg, Denmark). Electromyographic reflex responses were recorded from the middle of the biceps femoris and the rectus femoris muscles (surface silver–silver chloride electrodes). The EMG signal was amplified and filtered (1.5–150 Hz) by a Hellige (PPG Hellige GmbH, Germany) single channel EMG–EEG amplifier, recorded and analysed with NFRsys software (University of Aalborg, Denmark). The stimulation current was increased from 1 mA in steps of 1–2 mA until an ipsilateral reflex with an amplitude exceeding 20 μV for at least 10 ms was detected by the computer program. If a reflex was recorded three times at the same current intensity, this intensity was defined as the nociceptive reflex threshold to single stimulation. Maximal stimulation intensity was 80 mA. Eight reflexes, elicited with a stimulation intensity of 1.4 times the threshold intensity, were recorded, averaged and the root mean square (RMS) value in the 80–180-ms interval after the stimulus was calculated with EPsys software (University of Aalborg, Denmark). The volunteer then rated the perceived pain of the eight stimulations on a 10-cm visual analogue scale (VAS).

NOCICEPTIVE REFLEX THRESHOLD TO REPEATED STIMULI

The sural nerve was stimulated as described above, but the single stimulus was repeated five times with a frequency of 2 Hz, as described by Arendt-Nielsen and colleagues [13, 14]. Current intensity was increased from 1 mA in steps of 1–2 mA until a psychophysical or electrophysiological summation was detected by the computer program. The summation thresholds were defined as an increase in pain during the five stimulations (psychophysical summation threshold) or an increase in amplitude of the last one or two reflexes above a fixed limit of 20 μV for at least 10 ms (electrophysiological summation threshold). Maximal stimulation intensity was 80 mA.

MECHANICAL PRESSURE PAIN DETECTION AND PAIN TOLERANCE THRESHOLDS

Pressure pain detection and pain tolerance thresholds were measured on the centre of the pulp of the second (pain detection) and third (pain tolerance) finger of the right hand with an electronic pressure algometer (Somedic AB, Stockholm, Sweden) [15–17]. A probe with a surface area of 0.28 cm^2 was used, and the pressure increase was 30 kPa s^{-1}. Pain detection was defined as the point when pressure turned into pain, and pain tolerance as the point when the volunteer did not want the pressure to be increased further. For determination of both thresholds, the mean of two consecutive measurements was used.

REACTION TIME

A 1000-Hz tone was delivered from a computer with randomized intervals of 3–8 s, and a timer was started simultaneously. The volunteer was told to press a button as fast as possible after each tone. Reaction time was defined as the time from the tone until the volunteer pressed the button. The mean of three consecutive measurements was used.

EVOKED POTENTIALS

Argon laser stimulation

A 200-ms stimulus and a 3-mm laser beam diameter were used. Laser stimuli were applied to the dorsum of the hand (C7 dermatome). Repeated stimulation in the same area was avoided. The pain threshold was defined as a distinct sharp pinprick, and was calculated as the mean of five ascending and five descending series of stimulations. A laser stimulus of 1.4 times the initial pain threshold was used as stimulation for recording of the evoked potentials.

Electrical stimulation

An intracutaneous electrode, as described by Bromm and Meier [4], was used. The finger pulp of the third or fourth finger was stimulated with a blunt 1-mm steel pin electrode, with a digital ring finger electrode placed proximal as reference. A 25-ms, train-of-five, 1-ms, square-wave impulse (perceived as a single stimulus) delivered from a Digitimer DS7 constant current stimulator (Digitimer Ltd, UK) triggered by a Phillips PM5150 Generator (Phillips GmbH, Germany) was used as stimulus. The horn layer of the epidermis was scraped carefully in a 2 × 2-mm area. Intracutaneous placement was accepted when a stimulation current of less than 0.5 mA was felt as a distinct pinprick. The current was increased from 0 in steps of 0.2 mA until the volunteer scored the stimulus (VAS) as painful as the laser stimulus of 1.4 times the initial laser pain threshold. This intensity was used for recording of the electrical evoked potentials.

Auditory stimulation

Auditory evoked potentials were elicited by click stimulation (Medelec ST 10, Medelec Ltd, UK) with 90 dB applied binaural through acoustically shielded headphones.

Recording

The evoked vertex potentials were recorded from a needle electrode (scalp electrode, 0.3 × 10 mm, Dantec, Denmark), inserted at Cz′ *vs* a surface silver–silver chloride electrode on the right mastoid. The signal, in the interval of 0.5 s before the stimulus until 2 s after the stimulus, was amplified and filtered (0.1–30 Hz) with a Hellige (Hellige AG, Germany) single-channel EEG amplifier and recorded, averaged and analysed with EPsys software (University of Aalborg, Denmark). Evoked potentials from 16 stimulations were averaged.

Perceived pain from laser and electrical stimulations

After each series of 16 laser or electrical stimulations, volunteers rated perceived pain on a 10 cm VAS.

MEDICATION

Volunteers were tested on two different days, at least 1 week apart. They received, in randomized order, alfentanil on one day and propofol on the other. The medication was prepared by an anaesthetist who monitored the volunteer and study but did not take part in the measurements. The volunteer and other investigators were blinded as to the medication.

The first concentration of alfentanil (low dose) was attained by a loading dose of 7.5 $\mu g\ kg^{-1}$ i.v. followed by an infusion of 0.1 $\mu g\ kg^{-1}\ min^{-1}$ and the second (high dose) by a loading dose of 15 $\mu g\ kg^{-1}$ i.v. followed by an infusion of 0.3 $\mu g\ kg^{-1}\ min^{-1}$. The first propofol concentration (low dose) was attained by a loading dose of 0.5 $mg\ kg^{-1}$ i.v. followed by an infusion of 10 $\mu g\ kg^{-1}\ min^{-1}$ and the second (high dose) by a loading dose of 1 $mg\ kg^{-1}$ i.v. followed by an infusion of 30 $\mu g\ kg^{-1}\ min^{-1}$.

EXPERIMENTAL DESIGN

The tests were explained to the volunteer and a trial testing was performed in order to familiarize the volunteer with the procedure. Thereafter a baseline test series was performed. Further test series were performed 20 min after each loading dose during the infusion.

STATISTICAL ANALYSIS

The Friedman test for repeated measures analysis of variance on ranks, and the Student–Newman–Keuls test for multiple comparisons were used for statistical analysis. $P < 0.05$ was considered significant.

Results

NOCICEPTIVE REFLEX (TABLE 1)

The threshold for nociceptive reflex to single stimulations was increased significantly by propofol and alfentanil compared with baseline, but there was no difference in the increase caused by propofol or alfentanil. The RMS of the recorded reflex was decreased significantly by propofol and alfentanil compared with baseline, but the high dose of propofol decreased the RMS significantly more than the high dose of alfentanil. The perceived pain to stimulations with a current intensity of 1.4 times the baseline threshold intensity was not decreased by propofol, whereas alfentanil produced a significant decrease in pain intensity compared with baseline. Propofol did not change the psychophysical or electrophysiological threshold for summation of the nociceptive reflex, but both thresholds were increased significantly by alfentanil compared with baseline and the difference between high-dose propofol and high-dose alfentanil was significant.

MECHANICAL PRESSURE (TABLE 1)

The pressure pain detection thresholds tended to be decreased by propofol and increased by alfentanil, but differences from baseline were not significant. However, the difference between high-dose propofol and high-dose alfentanil was significant. The pressure pain tolerance thresholds were decreased significantly by propofol at the high dose, whereas alfentanil increased significantly the threshold at the high dose compared with baseline. The difference between high-dose propofol and high-dose alfentanil was significant.

REACTION TIME (TABLE 1)

Both propofol and alfentanil increased the reaction time compared with baseline, but a significantly larger increase was found with high-dose propofol compared with high-dose alfentanil.

EVOKED VERTEX POTENTIAL LATENCIES (TABLE 2)

A typical evoked vertex potential (laser) is shown in figure 1. Neither propofol nor alfentanil changed the latencies of the vertex evoked potentials, except for N1 latency at the high propofol concentration (increase of 10 % compared with baseline and 16 % compared with high-dose alfentanil).

Table 1 Numerical results from experimental pain tests and reaction time. All values are median (5–95 percentiles), and are expressed as percentage change from baseline (baseline = 100%). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, L = low concentration, H = high concentration

	Propofol			Alfentanil	
Test	Low concn	High concn	Comparison P–A	Low concn	High concn
Nociceptive reflex threshold	125.0 (85.7–162.5) *B, *H	200.0 (79.3–270.5) *B, *L	ns (PL–AL) ns (PH–AH)	115.4 (93.5–161.2) *B, *H	140.0 (73.9–235.4) *B, *L
Nociceptive reflex RMS	63.2 (34.6–151.9) *B, *H	25.3 (10.7–136.6) *B, *H	ns (PL–AL) *(PH–AH)	81.0 (26.3–105.6) *B	56.1 (15.0–150.8) *B
Nociceptive reflex VAS	100.0 (63.7–117.5) ns	85.4 (60.2–126.6) ns	ns (PL–AL) *(PH–AH)	94.6 (61.5–102.9) *H	78.4 (49.3–101.1) *B, *H
Nociceptive reflex summation psychophysical threshold	104.5 (82.2–131.7) ns	104.5 (87.8–142.6) ns	ns (PL–AL) *(PH–AH)	100.0 (100.0–158.7) *H	127.3 (100.0–215.8) *B, *L
Nociceptive reflex summation electrophysiological threshold	100.0 (84.0–123.9) ns	109.7 (76.4–142.3) ns	ns (PL–AL) *(PH–AH)	109.1 (100.0–128.5) *H	133.3 (100.4–214.2) *B, *L
Pressure pain threshold	90.8 (69.9–115.2) ns	81.8 (73.0–116.6) ns	ns (PL–AL) *(PH–AH)	100.6 (69.8–140.6) ns	115.6 (84.1–163.5) ns
Pressure pain tolerance	97.3 (84.9–110.0) *H	87.2 (70.2–100.8) *B, *L	ns (PL–AL) *(PH–AH)	109.0 (85.0–121.3) *H	117.4 (85.5–136.3) *B, *L
Reaction time	120.1 (77.0–156.2) *H	123.8 (108.5–235.5) *B, *L	ns (PL–AL) *(PH–AH)	109.5 (101.1–134.6) *B	112.7 (98.1–192.1) *B

Table 2 Numerical results from latencies of the evoked potentials (EP). All values (ms) are median (5–95 percentiles). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, B = baseline, L = low concentration, H = high concentration

	Propofol				Alfentanil		
Test	Baseline	Low concn	High concn	Comparison P–A	Baseline	Low concn	High concn
Laser EP latencies P1	320 (258–382) ns	305 (259–343) ns	324 (222–366) ns	ns (PL–AL) ns (PH–AH)	313 (242–382) ns	320 (228–373) ns	320 (252–352) ns
Laser EP latencies N1	445 (414–492) *H	442 (376–525) *H	488 (387–565) *B, *L	ns (PL–AL) *(PH–AH)	438 (376–514) ns	430 (375–461) ns	422 (360–477) ns
Laser EP latencies P2	641 (492–740) ns	633 (511–763) ns	648 (572–876) ns	ns (PL–AL) ns (PH–AH)	594 (541–664) ns	633 (563–717) ns	641 (532–777) ns
Electrical EP latencies P1	152 (126–179) ns	156 (148–179) ns	148 (103–186) ns	ns (PL–AL) ns (PH–AH)	156 (141–180) ns	156 (133–194) ns	148 (141–202) ns
Electrical EP latencies N1	273 (207–318) ns	254 (228–358) ns	273 (213–397) ns	ns (PL–AL) ns (PH–AH)	281 (227–351) ns	266 (219–379) ns	266 (219–433) ns
Electrical EP latencies P2	434 (338–518) ns	450 (358–569) ns	445 (422–582) ns	ns (PL–AL) ns (PH–AH)	445 (423–634) ns	445 (438–614) ns	477 (319–659) ns
Auditory EP latencies P1	141 (118–155) ns	148 (117–156) ns	148 (126–163) ns	ns (PL–AL) ns (PH–AH)	141 (125–156) ns	148 (133–145) ns	155 (133–164) ns
Auditory EP latencies N1	231 (201–258) ns	227 (204–307) ns	219 (204–335) ns	ns (PL–AL) ns (PH–AH)	234 (203–304) ns	219 (203–326) ns	227 (211–320) ns
Auditory EP latencies P2	403 (368–518) ns	426 (275–459) ns	449 (322–498) ns	ns (PL–AL) ns (PH–AH)	422 (354–497) ns	453 (344–492) ns	453 (300–484) ns

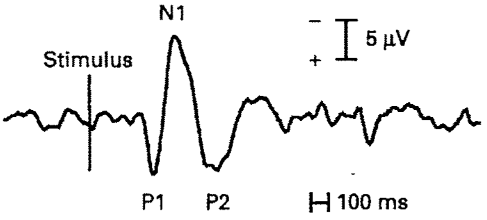

Figure 1 Laser evoked potential, which is the average of 16 evoked potentials elicited by short argon laser stimuli of 200 ms duration.

EVOKED VERTEX POTENTIAL AMPLITUDES (TABLE 3)

Neither propofol nor alfentanil changed the P1/N1 amplitudes of the laser evoked potentials. For the N1/P2 amplitudes of the laser evoked potentials and for the P1/N1 and N1/P2 amplitudes of the electrical and the auditory evoked potentials, both propofol and alfentanil reduced the amplitudes. In several cases (see table 3) propofol produced a significantly larger reduction than alfentanil. High-dose propofol and high-dose alfentanil induced the same amplitude reductions in the evoked potentials elicited by nociceptive stimuli (laser and electrical) as in the evoked potentials elicited by non-nociceptive stimuli (auditory) ($P = 0.12$ for P1/N1 amplitudes and $P = 0.21$ for N1/P2 amplitudes).

PERCEIVED PAIN TO LASER AND ELECTRICAL STIMULATIONS (TABLE 4)

Propofol did not reduce perceived pain (VAS scores) to laser and electrical stimulations, whereas high-dose alfentanil reduced significantly VAS scores

Table 3 Numerical results from amplitudes of the evoked potentials (EP). All values are median (5–95 percentiles), and are expressed as percentage change from baseline (baseline = 100 %). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, L = low concentration, H = high concentration

	Propofol			Alfetanil	
Test	Low concn	High concn	Comparison P–A	Low concn	High concn
Laser EP	97.8 (59.3–108.8)	81.2 (28.6–115.3)	ns (PL–AL)	96.0 (44.4–133.0)	91.3 (44.6–141.7)
amplitudes P1/N1	ns	ns	ns (PH–AH)	ns	ns
Laser EP	73.2 (27.1–110.7)	43.1 (22.3–71.5)	NS (PL–AL)	78.8 (58.1–125.7)	70.8 (41.2–132.1)
amplitudes N1/P2	*B, *H	*B, *L	*(PH–AH)	*B	*B
Electrical EP	54.7 (43.7–134.9)	45.5 (15.9–77.0)	*(PL–AL)	84.2 (67.4–148.6)	71.7 (23.6–132.1)
amplitudes P1/N1	*B, *H	*B, *L	*(PH–AH)	*H	*B, *L
Electrical EP	58.7 (30.0–76.9)	42.1 (32.7–67.8)	*(PL–AL)	92.0 (75.3–126.0)	78.6 (31.1–133.6)
amplitudes N1/P2	*B	*B	ns (PH–AH)	*B, *H	*B, *L
Auditory EP	70.7 (30.8–198.1)	46.1 (19.2–96.5)	*(PL–AL)	86.4 (66.6–103.4)	77.5 (52.3–85.7)
amplitudes P1/N1	*B	*B	ns (PH–AH)	*B, *H	*B, *L
Auditory EP	73.2 (27.1–110.7)	43.1 (22.3–71.5)	ns (PL–AL)	78.7 (58.1–125.7)	70.8 (41.2–132.1)
amplitudes N1/P2	*B, *H	*B, *L	*(PH–AH)	*B	*B

Table 4 Numerical results of perceived pain scores (VAS) from the laser and electrical evoked potentials (EP). All values are median (5–95 percentiles), and are expressed as percentage change from baseline (baseline = 100 %). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, L = low concentration, H = high concentration

	Propofol			Alfentanil	
Test	Low concn	High concn	Comparison P–A	Low concn	High concn
Laser EP VAS	94.9 (50.5–133.3)	100.8 (73.8–161.8)	ns (PL–AL)	95.2 (62.9–131.1)	83.8 (45.2–109.4)
	ns	ns	ns (PH–AH)	*H	*B, *L
Electrical EP VAS	97.2 (56.5–133.1)	94.1 (45.2–122.2)	ns (PL–AL)	95.9 (35.2–120.1)	75.5 (23.9–122.9)
	ns	ns	*(PH–AH)	*H	*B, *L

compared with baseline and low-dose alfentanil. VAS scores were also significantly smaller for high-dose alfentanil compared with high-dose propofol.

Discussion

We have shown that sedation can influence both the psychophysical and electrophysiological responses of some experimental pain tests used to measure analgesic efficacy. Propofol increased the threshold of the nociceptive reflex to single stimulations and decreased the amplitude of the evoked potentials elicited by nociceptive laser and electrical stimulations. This indicates that these may not, under all circumstances, assess the excitability of the nociceptive system. Propofol, in subhypnotic doses, had no analgesic effect on painful electrical and heat stimulations, but had a hyperalgesic effect on pressure pain.

NOCICEPTIVE REFLEX

Willer [18] investigated the relation between nociceptive reflex and perceived pain. The occurrence of the reflex was related closely to the pain threshold, and a linear relation was found between perceived pain and amplitude of the nociceptive reflex. This finding was confirmed later by Chan and Dallaire [19]. The reflex threshold to single stimuli has been found to increase with i.v. morphine [20], extradural morphine [21], i.m. alfentanil [22], but also with the weaker, non-opioid analgesics ketoprofen [23] and acetylsalicylic acid [24]. This indicates that the nociceptive reflex to single electrical stimulations of the sural nerve can be used to demonstrate analgesia produced by pure analgesic drugs. However, sub-anaesthetic (0.10–0.26 vol % end-tidal) isoflurane concentrations significantly increase the threshold for nociceptive reflex to single stimuli, but do not change the reaction to pain elicited by heat, cold or pressure, or the threshold of the nociceptive reflex to repetitive stimuli [5]. Training and attention has been shown to influence the pain threshold and the threshold for the nociceptive reflex [2], and distraction has been shown to decrease the nociceptive reflex [25]. In this study, propofol, in sedative doses, produced the same increase in the nociceptive reflex threshold to single stimulations as alfentanil, but showed hyperalgesic effects for tolerance to mechanical pressure. This indicates that the increase in threshold of the nociceptive reflex could be caused by sedation and not analgesia. The nociceptive reflex to single electrical stimulations may therefore not be a measure of analgesia when the drug tested also has sedative effects. As the nociceptive reflex has a sensory afferent and motor efferent component, the difference between propofol and alfentanil could be explained by stronger depression of the motor component by propofol. However, this would influence reflexes elicited by single and repeated stimulations in the same manner. Propofol did not change the threshold for temporal summation of the nociceptive reflex to repeated stimulations, indicating that the muscle component is not influenced significantly by propofol.

MECHANICAL PRESSURE

Early studies by Clutton-Brock [8, 26] and Dundee [9], using a relatively simple mechanical pressure pain model showed that small doses of thiopentone had a hyperalgesic effect. Our study showed that propofol, in subhypnotic doses, had a similar hyperalgesic effect on pressure pain. *In vitro* studies in single neurones [27] and isolated spinal cord models [10] showed that propofol and thiopentone depressed spinal nociceptive transmission, but they may have a different effect, through GABA inhibitory neurones, in the intact animal or human [28].

EVOKED VERTEX POTENTIALS

Arendt-Nielsen [3] correlated the amplitude or power of the long latency evoked vertex potential to an argon laser nociceptive thermal stimulation with the intensity of the perceived pain. With this method an analgesic effect of alfentanil [29], ibuprofen [30], paracetamol [31], codeine [32] and extradural morphine [33] has been demonstrated. A recent study failed to show an effect on laser evoked potentials of i.v. morphine [34]. In a recent review on nociceptive laser evoked vertex potentials by Arendt-Nielsen [35], it was suggested that sedation might influence the evoked potential. Evoked potentials to non-nociceptive stimuli should therefore be recorded as a control for sedation. We have shown recently that subanaesthetic isoflurane concentrations (0.10–0.26 vol% end-tidal) also decreased the amplitude of the evoked vertex potentials to painful laser and electrical stimuli [6]. But isoflurane produced a similar reduction in the amplitude of non-pain related auditory evoked vertex potentials recorded with the same paradigm, and did not reduce the perceived pain. In our study, propofol reduced the amplitude of evoked vertex potentials, but showed a hyperalgesic effect in the pain tolerance threshold to mechanical. This indicates that the reduction in amplitude of evoked vertex potentials by propofol and isoflurane is not caused by an analgesic effect. Anker-Møller and co-workers [7] also found a decrease in laser evoked vertex potentials with subhypnotic doses of thiopentone and propofol, but they did not measure the effect on non-pain-related potentials.

DRUG CONCENTRATIONS

The concentrations of propofol and alfentanil used in this study were chosen on empirical grounds, so that the low doses produced slight sedation (propofol) and slight analgesia (alfentanil), and the high doses distinct sedation and analgesia. The reaction time for low-dose propofol was slightly but not statistically increased compared with baseline, but for the high dose a significant increase was found compared with baseline and low-dose propofol. Low-dose alfentanil produced a slight but not significant increase in pain tolerance to mechanical pressure, but for the high dose of alfentanil a significant increase was found compared with baseline and the low dose. Furthermore, the threshold for the nociceptive reflex to single stimulations, and the decrease in the amplitude of the vertex potentials were not different for high-dose propofol and high-dose alfentanil. This indicates that the chosen doses were relevant according to the initial criteria, and that an effect of sedation on the nociceptive reflex and the amplitude of the vertex potentials could be investigated at these concentrations.

SHORT *VS* REPEATED OR LONGER LASTING STIMULATIONS

Arendt-Nielsen and co-workers [36, 37] and Brennum and co-workers [17, 38] have shown that brief localized nociceptive stimuli can be attenuated to a greater extent by extradural lignocaine or morphine than noxious stimulations of longer duration or involving larger areas. That central temporal and spatial summation of nociceptive stimuli are important for determination of anaesthetic efficacy is supported by our study. The responses to experimental pain tests involving short or single stimulations were influenced by the sedative effect of propofol, whereas tests involving longer lasting or repeated stimulations were not. Alfentanil showed the expected analgesia on both the short or single stimulations, and the longer lasting or repeated stimulations used in this study (these results are in accordance with previous studies [22, 29]).

PAIN DETECTION *VS* PAIN TOLERANCE THRESHOLDS

Measuring pain tolerance thresholds and not just pain detection was also important in this study. If we had only measured pain detection thresholds to mechanical pressure, we would not have detected the hyperalgesic effect of propofol on mechanical pain.

This study showed that when experimental pain models were used to measure an analgesic effect, the effects of sedation on both psychophysical and electrophysiological responses must be controlled. It is important to combine threshold measurements and electrophysiological responses with psychophysical pain ratings. Furthermore, models eliciting temporal or spatial summation, or both, of nociceptive stimuli appear to be less influenced by sedation.

Acknowledgement

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References

1. De Broucker T, Willer JC, Bergeret S. The nociceptive flexion reflex in humans: A specific and objective correlate of experimental pain. In: Chapman CR, Loeser JD, eds. *Issues in Pain Measurement*. New York: Raven Press, 1989; 337–352.
2. Willer JC. Nociception flexion reflex as a physiological correlate of pain sensation in humans. In: Bromm B, ed. *Pain Measurements in Man. Neurophysiological Correlates of Pain*. Amsterdam: Elsevier, 1984; 87–110.
3. Arendt-Nielsen L. First pain event related potentials to argon laser stimuli: recording and quantification. *Journal of Neurology, Neurosurgery and Psychiatry* 1990; 53: 398–404.
4. Bromm B, Meier W. The intracutaneous stimulus: a new pain model for algesimetric studies. *Methods and Findings in Experimental and Clinical Pharmacology* 1984; 6: 405–410.
5. Petersen-Felix S, Bak P, Arendt-Nielsen L, Fischer M, Bjerring P, Roth D, Zbinden AM. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by

experimentally induced pain. *British Journal of Anaesthesia* 1995; **75**: 55–60.

6. Roth D, Petersen-Felix S, Fischer M, Bak P, Arendt-Nielsen L, Bjerring P, Zbinden AM. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials. *British Journal of Anaesthesia* 1996; **76**: 38–42.
7. Anker-Møller E, Spangsbjerg N, Arendt-Nielsen L, Schultz P, Kristensen MS, Bjerring P. Subhypnotic doses of thiopentone and propofol cause analgesia to experimentally induced acute pain. *British Journal of Anaesthesia* 1991; **66**: 185–188.
8. Clutton-Brock J. Some pain threshold studies with particular reference to thiopentone. *Anaesthesia* 1960; **15**: 71–72.
9. Dundee JW. Alterations in response to somatic pain associated with anaesthesia II: the effect of thiopentone and pentobarbitone. *British Journal of Anaesthesia* 1960; **32**: 407–414.
10. Jewett BA, Gibbs LM, Tarasiuk A, Kendig JJ. Propofol and barbiturate depression of spinal nociceptive neurotransmission. *Anesthesiology* 1992; **77**: 1148–1154.
11. Wilder-Smith OHG, Kolletzki M, Wilder-Smith CH. Sedation with intravenous infusions of propofol or thiopentone. Effects on pain perception. *Anaesthesia* 1995; **50**: 218–222.
12. Stein C, Morgan MM, Leibeskind JC. Barbiturate-induced inhibition of a spinal nociceptive reflex: role of GABA mechanisms and descending modulation. *Brain Research* 1987; **407**: 307–311.
13. Arendt-Nielsen L, Brennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of central temporal summation of the human nociceptive system. *European Journal of Applied Physiology* 1994; **68**: 266–273.
14. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of *N*-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesthesia and Analgesia* 1995; **81**: 63–68.
15. Brennum B, Kjeldsen M, Jensen K, Jensen TS. Measurement of human pressure–pain thresholds on fingers and toes. *Pain* 1989; **38**: 211–217.
16. Dahl JB, Rosenberg J, Molke Jensen F, Kehlet H. Pressure pain thresholds in volunteers and herniorrhaphy patients. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 673–676.
17. Brennum J, Arendt-Nielsen L, Secher NH, Jensen TS, Bjerring P. Quantitative sensory examination in human epidural anaesthesia and analgesia: effects of lidocaine. *Pain* 1992; **51**: 27–34.
18. Willer JC. Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain* 1977; **3**: 69–80.
19. Chan CWY, Dallaire M. Subjective pain sensation is linearly correlated with the flexion reflex in man. *Brain Research* 1989; **479**: 145–150.
20. Willer JC. Studies on pain. Effects of morphine on a spinal nociceptive flexion reflex and related pain sensation in man. *Brain Research* 1985; **331**: 105–114.
21. Willer JC, Bergeret S, Gaudy JH. Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. *Anesthesiology* 1985; **63**: 675–680.
22. Petersen-Felix S, Arendt-Nielsen L, Bak P, Bjerring P, Breivik H, Svensson P, Zbinden AM. Ondansetron does not inhibit the analgesic effect of alfentanil. *British Journal of Anaesthesia* 1994; **73**: 326–330.
23. Willer JC, De Broucker T, Bussel B, Roby-Brami A, Harrewyn JM. Central analgesic effect of ketoprofen in humans: electrophysiological evidence for a supraspinal mechanism in a double-blind cross-over study. *Pain* 1989: **38**: 1–7.
24. Willer JC, Bathien N. Pharmacological modulations on the nociceptive flexion reflex in man. *Pain* 1977; **3**:111–119
25. Willer JC, Boureau F, Albe-Fessard D. Supraspinal influences on nociceptive flexion reflex and pain sensation in man. *Brain Research* 1979; **179**: 61–68.
26. Clutton-Brock J. Pain and the barbiturates. *Anaesthesia* 1961; **16**: 80–88.
27. Kitahata LM, Ghazi-Saidi K, Yamashita M, Kosaka Y, Bonikos C, Taub A. The depressant effect of halothane and sodium thiopental on the spontaneous and evoked activity of dorsal horn cells: lamina specificity, time course and dose dependence. *Journal of Pharmacology and Experimental Therapeutics* 1975; **195**: 515–521.
28. Kitahata LM, Saberski L. Are barbiturates hyperalgesic? *Anesthesiology* 1992; **77**: 1059–1061.
29. Arendt-Nielsen L, Øberg B, Bjerring P. Analgesic efficacy of i.m. alfentanil. *British Journal of Anaesthesia* 1990; **65**: 164–168.
30. Nielsen JC, Bjerring P, Arendt-Nielsen L, Petterson KJ. A double-blind placebo controlled, cross-over comparison of the analgesic effect of ibuprofen 400 mg and 800 mg on laser-induced pain. *British Journal of Clinical Pharmacology* 1990; **30**: 711–715.
31. Nielsen JC, Bjerring P, Arendt-Nielsen L, Petterson KJ. Analgesic efficacy of immediate and sustained release paracetamol and plasma concentrations of paracetamol. Double blind, placebo-controlled evaluation using painful laser stimulation. *European Journal of Clinical Pharmacology* 1992; **42**: 261–264.
32. Sindrup SH, Brøsen K, Bjerring P, Arendt-Nielsen L, Larsen U, Angelo HR, Gram LF. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of spartine. *Clinical Pharmacology and Therapeutics* 1990; **48**: 686–693.
33. Arendt-Nielsen L, Øberg B, Bjerring P. Hypoalgesia following epidural morphine: a controlled quantitative experimental study. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 430–435.
34. van der Burght M, Elkjær Rasmussen S, Arendt-Nielsen L, Bjerring P. Morphine does not affect laser induced warmth and pin prick pain thresholds. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 161–164.
35. Arendt-Nielsen L. Characteristics, detection, and modulation of laser-evoked vertex potentials. *Acta Anaesthesiologica Scandinavica* 1994; **38** (Suppl. 98).
36. Arendt-Nielsen L, Øberg B, Bjerring P. Quantitative assessment of extradural bupivacaine analgesia. *British Journal of Anaesthesia* 1990; **65**: 633–638.
37. Arendt-Nielsen L, Anker-Møller E, Bjerring P, Spangsberg N. Onset phase of spinal bupivacaine analgesia assessed quantitatively by laser stimulation. *British Journal of Anaesthesia* 1990; **65**: 639–642.
38. Brennum J, Arendt-Nielsen L, Horn A, Secher NH, Jensen TS. Quantitative sensory examination during epidural anaesthesia and analgesia in man: effects of morphine. *Pain* 1993; **52**: 75–83.

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Quantitative EEG in assessment of anaesthetic depth: comparative study of methodology†

C. E. THOMSEN AND P. F. PRIOR

Summary

Methodology for assessment of depth of anaesthesia based on analysis of the electroencephalogram (EEG) is controversial. Techniques range from display of single measures, for example median value of the frequency spectrum, to dedicated pattern recognition systems based on measures of several EEG features. We have compared the performance of four techniques using tape-recorded data from 23 patients anaesthetized with either halothane or isoflurane using standardized regimens. The techniques were: (1) median frequency, (2) spectral edge frequency, (3) the cerebral function analysing monitor (CFAM1) and (4) a depth of anaesthesia monitor based on EEG pattern recognition (ADAM). Dose–response curves are presented for stepwise increases in stable end-tidal concentrations of each agent. Results indicated considerable inter-patient variability and the limitations of single EEG measures, particularly with deeper anaesthesia producing a burst suppression pattern in the EEG. Pattern recognition techniques reduced these difficulties and appeared to be promising over a wide range of anaesthetic levels. (*Br. J. Anaesth.* 1966; **77**: 172–178)

Key words

Monitoring, electroencephalography. Anaesthesia, depth. Memory. Anaesthetics volatile, isoflurane. Anaesthetics volatile, halothane.

A simple objective method for assessment of depth of anaesthesia would be a useful facility in anaesthetic practice. The magnitude of the clinical problem of "awareness" during anaesthesia is now thought to be of the order of 1:1000 [1, 2]. The most appropriate means of recognizing it remains more controversial [2, 3].

The electroencephalogram (EEG) provides a direct measure of the functional state of the brain, permitting warning of the risk of awareness and detection of unnecessarily deep anaesthesia [4]. Blood or end-tidal concentrations of anaesthetic have been known for many years to show close correlations with EEG variables over the middle ranges of anaesthetic depth, leading to early attempts at automatic control [5]. In addition to questions of practicality, the use of EEG monitoring of anaesthesia remains debatable for three reasons: (i) EEG changes during anaesthesia tend to be agent-specific, (ii) the underlying principles of appropriate methods for monitoring have received only limited attention [6–10], (iii) the different techniques have rarely been subjected to rigorous comparative investigation [11, 12]. In this study we have compared the performance of four techniques of EEG monitoring for analysis of data tape-recorded from 23 patients anaesthetized with halothane or isoflurane. These are: median frequency (MF) [13, 14], spectral edge frequency (SEF) [15], the cerebral function analysing monitor (CFAM1) [8, 16] and the advanced depth of anaesthesia monitor (ADAM) [17–19]. The first two methods monitor single EEG features, while the latter two are essentially pattern recognition systems assessing multiple features.

Patients and methods

We were able to use EEG data recorded previously from 23 (ASA I) normotensive patients undergoing elective orthopaedic or gynaecological surgery from the study of Lloyd-Thomas, Cole and Prior [20] during closely controlled, stable, stepwise increases in end-tidal concentrations of either halothane or isoflurane.

The raw EEG data from left and right parietal regions were recorded originally on analogue tape simultaneously with the processing by the CFAM1 monitor [20]. The tapes have now been re-analysed using the ADAM system and comparisons with the original CFAM1 analysis are presented.

After Ethics Committee approval for the original study [20], premedication comprised papaveretum 0.2 mg kg^{-1} and hyoscine 4 μg kg^{-1} i.m., 90 min before anaesthesia. This was followed by induction with thiopentone 5 mg kg^{-1} and fentanyl 5 μg kg^{-1}. Tracheal intubation was performed after tubocurarine 0.5 mg kg^{-1}. Anaesthesia was maintained with either isoflurane or halothane and 66 % nitrous

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†A preliminary account of this work was presented to the IMIA-IFMBE Working Conference on "Biosignal Interpretation", Aalborg, Denmark, August 1993 [22].

oxide in oxygen. End-tidal carbon dioxide was maintained at 5%. If systolic arterial pressure decreased to less than 100 mm Hg, anaesthesia was lightened, and data from that part of the recording rejected from analysis, to avoid any possibility of unwanted effects of hypotension.

Twelve patients received isoflurane at end-tidal concentrations of 0.5, 1.0, 1.5 and 2.0 vol% and 11 patients received halothane at end-tidal concentrations of 0.5, 1.0 and 1.5 vol%. Artefact-free samples of 5 min duration were obtained during the control period with nitrous oxide in oxygen after a stabilization period of 15–20 min at each end-tidal concentration of the volatile agent and during recovery.

SIGNAL PROCESSING

The paper traces of the original unprocessed EEG were used to select artefact-free samples corresponding precisely to the marked periods analysed in the original study [20]. These were studied with the following methods of analysis.

Median and spectral edge frequencies

Median (MF) and spectral edge (SEF) frequencies were calculated as the 50th and 95th centiles of the accumulated value of the EEG power spectrum using the integrated frequency analysis in the ADAM system (fig. 1) based on 10th order autoregressive modelling.

Cerebral function analysing monitor (CFAM1)

After passage through an asymmetric band-pass filter, EEG amplitude and frequency were analysed digitally. The results were stored as numerical data and plotted on a screen and on paper. The clinician interpreted the charted results of analysis against an unprocessed EEG display when required. Amplitude and its variations were displayed as the mean, 90th and 10th centiles and maxima and minima outside these values. Frequency analysis using a modified zero-crossing technique, indicated every 2 s the percentage of the total energy falling into the following bands: beta2 (> 20 Hz), beta1 (14.3–20 Hz), alpha2 (10–14.3 Hz), alpha1 (7.7–10 Hz), theta2 (5.3–7.7 Hz), theta1 (3.5–5.3 Hz), delta2 (2.0–3.5 Hz), delta1 (1–2 Hz) and very low frequency ($<$ 1 Hz), together with separate detection of percent time with EEG suppression ($< 3\ \mu$V RMS).

For this study the results of CFAM1 digital analysis of 2-s segments of the EEG were obtained from the previous work on the same tape-recorded data [20]. In addition, a "fast/slow EEG frequency ratio" was calculated: (beta2 + beta1 + alpha2 + alpha1)/(theta2 + theta1 + delta2 + delta1).

Advanced depth of anaesthesia monitor (ADAM)

This system was based on a pattern recognition system which uses calculations of probabilities derived from previously studied normal reference distributions of EEG from patients receiving isoflurane and halothane at different concentrations [17–19]. Contiguous 2-s periods of the EEG were passed through a filter which first, limited low-frequency components likely to be artefactual and second, counteracted the inherent skewed frequency/amplitude distribution of the EEG. The features extracted from each sample represented both spectral distribution and amplitude of the EEG. The system was trained by a pattern processing technique (unsupervised repetitive hierarchical cluster analysis) to produce a set of reference patterns for halothane and isoflurane [17–19]. Within each set the individual patterns were grouped and assigned colours to represent specific depths of anaesthesia so providing a simple "anaesthetic scale" divided into six levels: "drowsy" (dark blue), "very light" (light blue), "light" (green), "normal surgical" (yellow), "deep" (purple) and "very deep" (red) anaesthesia. Awake states, artefacts and movements were assigned to the "background colour" of the display. This colour coding bypassed the problem of interpreting agent-specific data, in that the same overall scale was displayed for the equivalent ranges even though the EEG patterns from which it was derived were different for each agent.

Both the class probability histograms (distribution of recognized reference EEG patterns) and the simultaneous colour-coded density spectral arrays (EEG frequency distribution) were plotted with a time resolution of 10 s, each point displayed on the chart being based on a weighted average over the immediately preceding period (approximately 30 s). EEG suppression was detected separately using a method based on time domain descriptors over 0.25-s periods. This enabled us to modify the original pattern recognition so that 2-s periods with suppressions of 0.25–0.75 s were assigned to "normal anaesthesia", those with suppression of 0.75–1.25 s to "deep anaesthesia" and those with suppression of 1.25–2.00 s to "very deep anaesthesia". To facilitate comparison with other monitoring techniques, the class probability histograms were converted to a single numerical value representing the depth of anaesthesia such that the value 6.0 represented "very deep" anaesthesia and 1.0 represented "drowsy". A value for anaesthetic depth was then calculated for each 10 s.

STATISTICAL ANALYSIS

An unpaired two-tailed *t* test was performed on the group data for each step in end-tidal concentration of each anaesthetic, that is control period nitrous oxide in oxygen *vs* +0.5% end-tidal concentration of inhaled anaesthetic, +0.5% *vs* +1.0%, etc. and +1.5% or +2.0% *vs* "recovery".

All group data are presented as dose–response curves of the digital values from the various monitor outputs and derived variables against the end-tidal concentrations of the volatile agents, and data are displayed as mean (SD). The significance of the change in mean value compared with the previous state is given above the second of each pair using the following notation: *$P < 0.01$, **$P < 0.001$, ***$P < 0.0001$; symbols in parentheses indicate significant

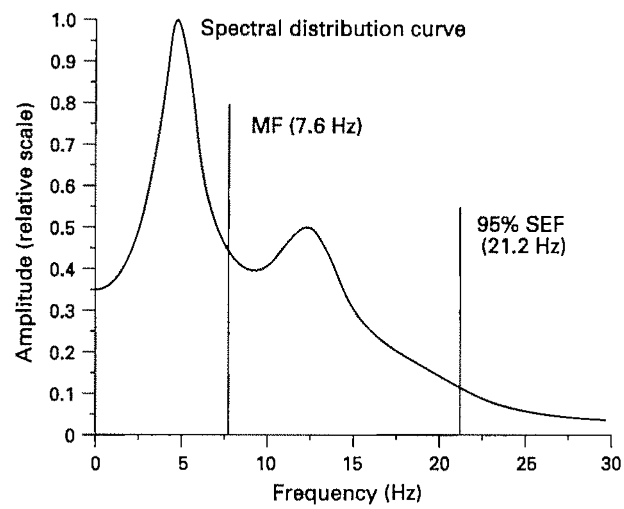

Figure 1 An example of power spectral analysis of an EEG segment during isoflurane anaesthesia. The spectral distribution was calculated using an autoregressive model of the 10th order. Each of the traditional single EEG measures, median frequency (MF) and spectral edge frequency (SEF), was derived from this curve, being the 50th and 95th centiles of the accumulated power value of the EEG frequency spectrum.

changes in the opposite direction to the overall trend for each variable (e.g. increased MF/SEF for increased anaesthetic depth).

Results

ISOFLURANE

The group data for MF (fig. 2) showed considerable inter-patient variability but this was less evident with increasing depth of anaesthesia up to an end-tidal concentration of 1.5%. From 1.5% to 2.0% there was no further change in MF. In contrast, the corresponding curve for SEF (fig. 3) did not exhibit a clear trend and inter-patient variability was high. Significant changes (decrease in SEF) were seen only from pure nitrous oxide in oxygen to +0.5% and from there to +1% end-tidal isoflurane concentration. With higher concentrations (+1.5%) SEF began to increase but thereafter (+2.0%) no further change occurred.

The CFAM1 amplitude data (fig. 4) replicated Bickford's 1950 work [5] showing an initial increase with light levels of anaesthesia and then a progressive decrease with increased depth of anaesthesia until burst suppression occurred. There was considerable variability in the CFAM1 group data and the only single frequency measures showing a continuous (but not significant for each step at $P < 0.01$) trend with increased depth of anaesthesia were theta1 and beta1. The calculated fast/slow ratio (fig. 5) based on the group data from the CFAM1 showed a clear trend up to +1.0% end-tidal concentration. However, a further increase produced only a small decrease in the fast-slow ratio. None the less, seen as group data this ratio did not, in contrast with other single EEG measures, reverse at +2.0% when two-thirds of patients developed burst suppression. Inter-patient variability was considerable, although it can only be indicated by the "standard deviation" bars shown in figure 5. Note that the standard

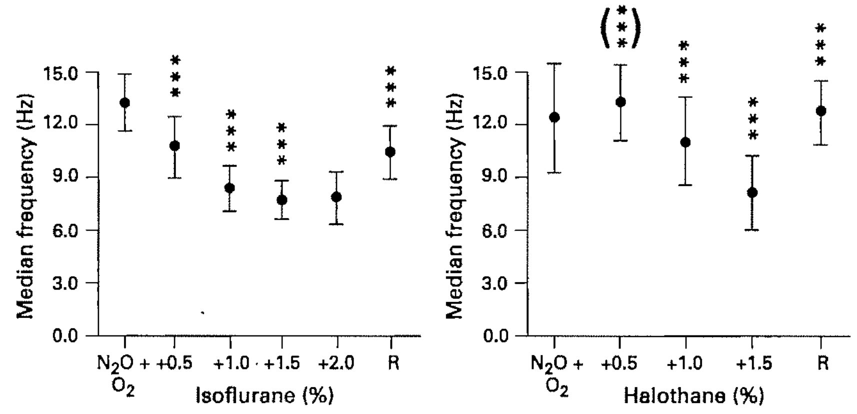

Figure 2 Median frequency; group data showing dose–response curves for patients receiving isoflurane ($n = 12$, left) and halothane ($n = 11$, right). The graphs show mean (SD) values during the sequence: nitrous oxide in oxygen ($N_2O + O_2$), step-wise increases in end-tidal concentration of the volatile agent and during recovery (R). The significance of changes in mean values (based on unpaired two-tailed t tests) compared with the previous state is given above the second of each pair using the following notation: *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$; symbols in parentheses indicate significant changes in the opposite direction to the overall trend for each variable (e.g. increased MF for increased anaesthetic depth).

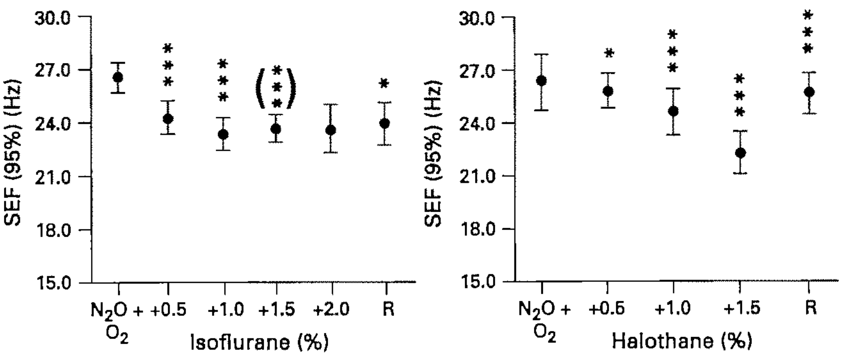

Figure 3 Spectral edge frequency (SEF); group data showing dose–response curves for patients receiving isoflurane ($n = 12$, left) and halothane ($n = 11$, right). Layout and symbols as in figure 2.

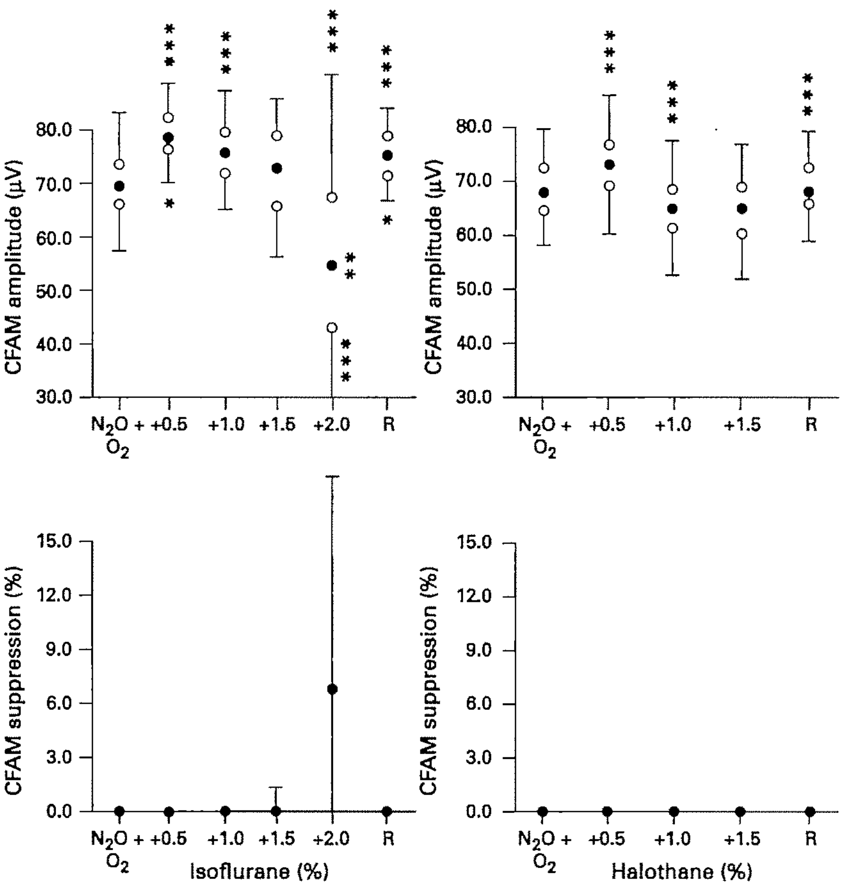

Figure 4 CFAM amplitude (top) and suppression (bottom); group data showing dose–response curves for patients receiving isoflurane ($n = 12$, left) and halothane ($n = 11$, right). Layout and symbols as in figure 2. CFAM1 amplitude values (peak-to-peak) are mean (●) and 90th and 10th centiles (○).

deviations are not legitimate for these CFAM1 group data as the frequency measures are based on pooled individual data and thereby not independent observations, and therefore no significance values could be calculated.

With the ADAM system (fig. 6), the group data showed highly significant and consistent trends with increasing end-tidal isoflurane concentrations, even though inter-patient variability was marked.

With most individual patients there was a clear initial decrease in MF towards deeper levels of anaesthesia with a relative low intra-patient variability. However, with increasing end-tidal concentrations of isoflurane from 1.5 to 2.0 %, MF showed a non-linear relationship in almost 50 % of patients, paradoxically suggesting "lightening" anaesthesia. Such patients all exhibited burst suppression patterns in the unprocessed EEG at an end-tidal isoflurane concentration of 2.0 % or, in some, even at 1.5 %. The corresponding SEF curves showed a poor correlation with increase in the end-tidal concentration. The spurious appearance of lightening of anaesthesia again occurred with burst suppression. Few of the individual curves produced a clear trend and inter-patient variability was high compared with the relatively small overall changes in SEF. Intra-patient variability was low, as with MF, but with small overall changes between different

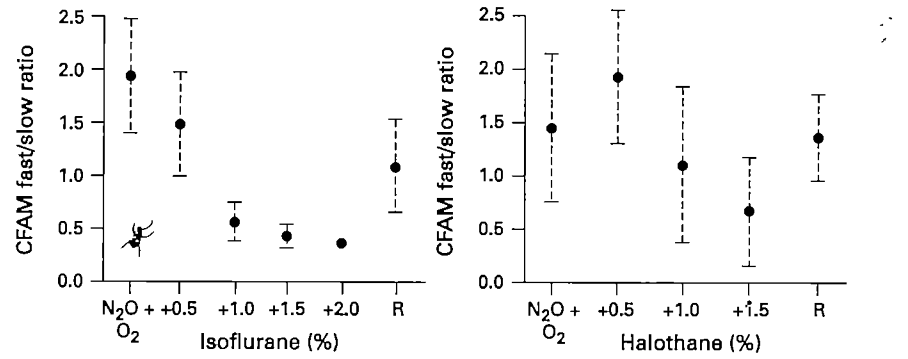

Figure 5 CFAM1 calculated fast/slow ratio; group data showing dose–response curves for patients receiving isoflurane ($n = 12$, left) and halothane ($n = 11$, right). Layout and symbols as in figure 2. The fast/slow EEG frequency ratio was calculated as (beta2 + beta1 + alpha2 + alpha1)/(theta2 + theta1 + delta2 + delta1). Note that SD, although indicated with dotted lines as a general guide, are not legitimate calculations as the frequency measures from the CFAM1 were based on pooled individual data and therefore not independent observations; thus no significance values could be calculated.

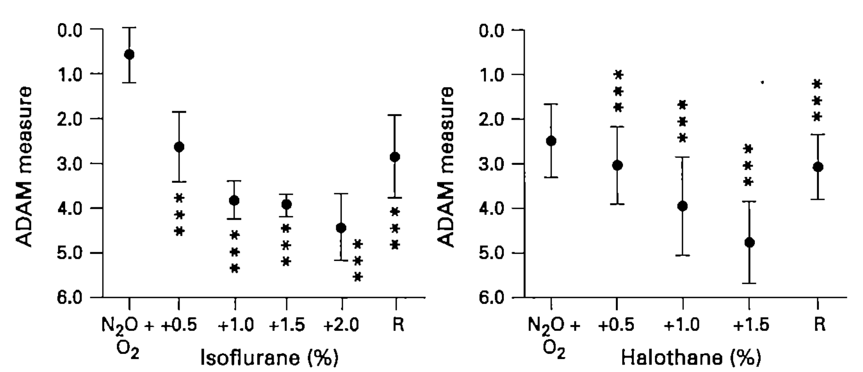

Figure 6 Anaesthetic depth, as indicated by the EEG pattern recognition system ADAM; group data showing dose–response curves for patients receiving isoflurane ($n = 12$, left) and halothane ($n = 11$, right). Layout and symbols as in figure 2. The scale on the vertical axis is based on a conversion of the class probability histograms to a single numerical value such that 0 is equivalent to the awake state, 1 to drowsiness, 2 to "very light" anaesthesia, 3 to "light" anaesthesia, 4 to "normal" surgical anaesthesia, 5 to "deep" and 6 to "very deep" anaesthesia.

anaesthetic concentrations. The CFAM1 showed, in all except one patient, an initial increase in amplitude with light levels of anaesthesia and then a progressive decrease with increasing end-tidal concentrations until onset of burst suppression. However, four patients not exhibiting burst suppression did not produce any further decrease in CFAM1 amplitude for 1.5 and 2.0% end-tidal concentrations. Intra-patient variability for CFAM1 amplitude was relatively low except during burst suppression, however, there was a considerable spread in absolute amplitude values between patients, indicating difficulties in producing a reliable measure of anaesthetic depth based solely on this feature.

The CFAM1 frequency measures showed marked intra- and inter-patient differences and the only consistent results were seen for beta1 + 2 and theta1 bands. EEG activity in the entire beta frequency band seemed significantly suppressed for moderate to deep levels of anaesthesia, but inter-patient variability for light levels was quite high. In most patients the theta1 band showed a clear trend to increase with increasing end-tidal concentrations. The calculated fast/slow ratio based on the pooled individual data from the CFAM1 decreased with end-tidal isoflurane concentrations up to 1% but in the majority of patients a further increase in end-tidal concentration produced only minor changes. For three patients an initial increase was seen in the fast/slow ratio comparable with that in the CFAM1 amplitude measures. In four patients there was a small increase in the fast/slow ratio during burst suppression at 2.0% end-tidal isoflurane. ADAM, the pattern-recognition system, showed consistent and uniform dose–response curves to approximately 1.5% in all except three patients with relatively low intra- and inter-patient variability. In these three patients the dose–response curve flattened just before short suppressions first appeared in the raw EEG, indicating difficulties in detection of the first signs of discontinuity in the EEG.

HALOTHANE

The group data for MF (fig. 2) showed inconsistency in trend and high inter-patient variability, even though changes for each step increase in halothane concentration were significant. The corresponding values for SEF (fig. 3) decreased progressively with increased end-tidal concentrations, but the changes for the first step (nitrous oxide in oxygen to +0.5%) were significant only at $P < 0.01$. The CFAM1 amplitude measures (fig. 4) showed only a non-significant trend with increasing halothane concentration and no EEG suppressions were detected in any patient. All CFAM1 frequency measures showed considerable variability as in the isoflurane study. The only frequency variables indicating a consistent trend with increased depth of anaesthesia were beta1+2 and, to a limited degree, theta1. However, although beta1 changed significantly ($P < 0.01$) for the first two steps, individual traces were variable. The calculated CFAM1 fast/slow ratio (fig. 5) showed a trend similar to MF, but the variability in EEG frequency changes with halothane reduced the potential value of this ratio. In contrast, the ADAM system (fig. 6) gave a near-linear relation with end-tidal concentration of halothane for group data but tended to overestimate the depth of anaesthesia for pure nitrous oxide in oxygen because of inconsistent initial changes in three patients (see below).

In individual patients, neither MF nor SEF produced a consistent trend with increasing end-tidal halothane concentrations. In four of 11 patients there was a decrease in MF and SEF after the period of nitrous oxide in oxygen alone, but it should be noted that inter-patient variability was considerable. Of the individual CFAM1 measures, none showed any significant trend with increased end-tidal concentration except for beta1+2 which, for all but two patients, appeared markedly suppressed for end-tidal concentrations of +1.5% or above. The individual CFAM1 amplitude dose–response curves were very variable with no consistent trend. No uniform pattern was evident with any of the CFAM1 frequency variables except theta1 which, in five of the patients increased with increasing end-tidal concentration. After an initial variable increase, the fast/slow ratio decreased in all patients with end-tidal concentrations greater than +1.5%. With the ADAM system there were more consistent trends but inter-patient variability was marked, especially compared with the isoflurane study. For three of the 11 patients, the ADAM system wrongly assessed pure nitrous oxide in oxygen effects as representing deeper anaesthesia than during +0.5% end-tidal concentration of halothane. A similar problem occurred in six patients for MF and in four for SEF.

Discussion

We have compared the performance of four different techniques for assessment of depth of anaesthesia with the volatile agents isoflurane and halothane using the same set of tape-recorded data obtained in a previous study [20]. As in other studies it was evident that methods using a single EEG feature are inadequate over the range of anaesthetic depths which include EEG burst suppression pattern [6, 12].

The CFAM1 had the advantage of displaying multiple features so that the user could identify individual changes with alterations in end-tidal concentration and, importantly, immediately recognize the burst suppression pattern. In addition to indicating deep anaesthesia, this pattern may have serious implications (e.g. hypoxia or ischaemia). However, it requires experience to learn the overall CFAM pattern combinations for each anaesthetic and with the launch of each new agent, further patterns would have to be assimilated. These considerations appear to have been addressed in a new version (CFAM3) about which preliminary information has been made available [personal communication, D. E. Maynard, 1995]. The development of the ADAM system uses a different approach where an unsupervised clustering technique is used to define a reference set of naturally occurring EEG patterns for different types and depths of anaesthesia. These reference patterns are then used in on-line pattern recognition during anaesthesia to display a simple-to-interpret, anaesthetic depth indicator. As yet the data base is relatively small and limited to the anaesthetic techniques on which it has been trained. We are presently completing studies to extend the anaesthetic database and on detection of changes caused by other aspects or complications of surgery and anaesthesia (asymmetries of any variables, distinction between deep anaesthesia, hypothermia and hypoxic–ischaemic complications).

The two examples of single EEG feature methods which we have investigated, MF and SEF, failed to characterize deepening anaesthesia when the burst suppression pattern had appeared in the EEG. Typically this EEG pattern was seen when end-tidal isoflurane concentrations were in the range +1.5 to +2.0%. This problem of burst suppression pattern in the EEG has not been addressed adequately by previous authors who have recommended single feature methods (MF or SEF) on the basis of studies which, while providing elegant correlations within the range of relatively low concentrations of various agents, have not included depths of anaesthesia normally associated with EEG suppressions [13, 14, 21]. Indeed some possibility of misclassification still exists with the ADAM system during early burst suppression. It should be noted that the CFAM1, in spite of the above mentioned problems regarding the complexity of a multivariate display, does clearly indicate even very early burst suppression patterns.

The limitations of single EEG measures for monitoring depth of anaesthesia have been indicated by others [6, 12] but the approach of using a pattern recognition system based on multiple features has received only limited attention [17–19] and has not previously been subjected to comparative studies. On the evidence of the results we believe it would be fruitful to explore such systems further. The techniques appear to have the potential of overcoming many of the difficulties previously associated with EEG monitoring of depth of anaesthesia. Moreover, on theoretical and practical grounds they are likely to be more generally applicable than methods based on evoked potential monitoring. Evoked potentials provide a crucially important tool for assessment of integrity of neural pathways during some spinal and intracranial surgical procedures. However, they require a skilled operator and their value for assessing anaesthetic depth in an individual patient appears to apply mainly to the lighter levels of anaesthesia.

Only when a highly reliable measure of depth of anaesthesia can be obtained in an individual patient will we achieve the aim of clinical acceptability.

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Dr A. R. Lloyd-Thomas generously allowed us to re-analyse tape-recorded data from his studies [20]. Dr R. M. Langford contributed with valuable suggestions and comments during preparation of the paper.

References

1. Lui WHD, Thorp TAS, Graham SG, Aitkenhead AR. Incidence of awareness with recall during general anaesthesia. *Anaesthesia* 1991; **46**: 435–437.
2. Jones JG. Perception and memory during general anaesthesia. *British Journal of Anaesthesia* 1994; **73**: 31–37.
3. Sandin R, Nordstrom O. Awareness during total i.v. anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 782–787.
4. Lunn JN, Rosen M, eds. *Consciousness, Awareness, Pain and General Anaesthesia*. London: Butterworths, 1987.
5. Bickford RG. Automatic electroencephalographic control of general anaesthesia. *Electroencephalography and Clinical Neurophysiology* 1950; **2**: 93–96.
6. Levy WJ. Intraoperative EEG patterns: implications for EEG monitoring. *Anesthesiology* 1984; **60**: 430–434.
7. Levy WJ. Effect of epoch length on power spectrum analysis of the EEG. *Anesthesiology* 1987; **66**: 489–495.
8. Prior PF, Maynard DE. *Monitoring Cerebral Function. Long-Term Monitoring of EEG and Evoked Potentials*. Amsterdam: Elsevier, 1987; 39–84.
9. Nuwer MR, Daube J, Fischer C, Schramm J, Yingling CD. Neuromonitoring during surgery. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology* 1993; **87**: 263–276.
10. Rodriguez RA, Edmonds HL jr, Schroeder JA. Quantitative EEG analysis during cardiac surgery in a case of spontaneous recall. *Electroencephalography and Clinical Neurophysiology* 1993; **87**: 250–253.
11. Levy WJ, Shapiro HM, Maruchak G, Meathe E. Automated EEG processing for intraoperative monitoring. *Anesthesiology* 1980; **53**: 223–236.
12. Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anesthesia. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 693–699.
13. Schwilden H, Stoeckel H. Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. *British Journal of Anaesthesia* 1987; **59**: 738–745.
14. Schwilden H, Schuttler J, Stoeckel H. Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. *Anesthesiology* 1987; **67**: 341–347.
15. Rampil IJ, Matteo RS. Changes in EEG spectral edge frequency correlate with hemodynamic response in laryngoscopy and intubation. *Anesthesiology* 1987; **67**: 139–142.
16. Maynard DE. Development of the CFM: the cerebral function analysing monitor (CFAM). *Annales Anesthesiologie Francaise* 1979; **20**: 253–255.
17. Thomsen CE, Christensen KN, Rosenfalck A. Computerized monitoring of depth of anaesthesia with isoflurane. *British Journal of Anaesthesia* 1989; **63**: 36–43.
18. Thomsen CE, Rosenfalck A, Nørregaard-Christensen K. Assessment of anaesthetic depth by clustering analysis and autoregressive modelling of electroencephalograms. *Computer Methods and Programs in Biomedicine* 1991; **34**: 125–138.
19. Thomsen CE. *Hierarchical Cluster Analysis and Pattern Recognition Applied to the Electroencephalogram—Development of ADAM (Advanced Depth of Anaesthesia Monitor)*. Aalborg: University of Aalborg, PhD thesis, 1992.
20. Lloyd-Thomas AR, Cole PV, Prior PF. Quantitative EEG and brainstem auditory evoked potentials: comparison of isoflurane with halothane using the cerebral function analysing monitor. *British Journal of Anaesthesia* 1990; **65**: 306–312.
21. Jessop J, Jones JG. Evaluation of the actions of general anaesthetics in the human brain. *General Pharmacology* 1992; **23**: 927–935.
22. Thomsen CE, Prior PF. Quantitative EEG in assessment of anaesthetic depth—a comparative study. In: Rosenfalck A, ed. *Proceedings of the IMIA-IFMBE Working Conference on "Biosignal Interpretation"*, Rebild Bakker, Aalborg, Denmark, August 25–27, 1993. Aalborg: Aalborg University, 1993; 164–168 (abstract).

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Spectral edge frequency of the electroencephalogram to monitor "depth" of anaesthesia with isoflurane or propofol

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Summary

To determine threshold values, sensitivity and specificity of the spectral edge frequency (SEF) of the electroencephalogram (EEG) that indicate intraoperative movements, we studied 49 patients undergoing elective laparotomy. Extradural analgesia was used in all patients. To maintain general anaesthesia, patients in group 1 ($n = 23$) received 0.4–1.2 vol% isoflurane and patients in group 2 ($n = 24$) propofol 3–5 mg kg^{-1} h^{-1} i.v. During operation and emergence from anaesthesia, spontaneous purposeful movements were documented. The EEG was recorded continuously in the awake state until the end of anaesthesia. Power spectral analysis calculated the SEF and power in the delta, theta, alpha and beta bands and the delta ratio. Adequate anaesthesia caused a statistically significant decrease in SEF from 16 to 12 Hz. Power in the beta band decreased and power in the theta band and total power increased compared with the awake state. Before and during movements observed in the intraoperative period or during emergence from general anaesthesia, SEF increased from 12 to 18 Hz, the power in beta band increased and theta power decreased compared with the state of adequate anaesthesia. A threshold value of SEF 14 Hz to predict movements during anaesthesia had a sensitivity of 72% and specificity of 82%. (*Br. J. Anaesth.* 1996; **77**: 179–184)

Key words

Anaesthetics i.v., propofol. Anaesthetics volatile, isoflurane. Brain, electroencephalography. Monitoring, electroencephalography. Anaesthesia, depth. Memory.

Many general anaesthetics change the spontaneous activity of the electroencephalogram (EEG) from low voltage fast wave to high voltage slow wave patterns progressively with increasing serum or end-expiratory concentrations. Burst suppression patterns may occur at very high doses of some general anaesthetics [1]. With power spectral analysis of the EEG signal, single variables could be derived from the native EEG, such as spectral edge frequencies (SEF), for example SEF 95, SEF 90, SEF 50 = median frequency [2, 3]; the spectral edge frequency is the frequency below which 95%, 90% or 50%, respectively, of the total EEG power is located. SEF 95, 90 and median frequency (SEF 50) are reduced with increasing serum or end-tidal concentrations of many general anaesthetics or opioid analgesics [4–11]. Furthermore, it has been suggested that SEF may be used to measure depth of anaesthesia and indicate arousal during emergence from general anaesthesia [12–14]. Nevertheless, SEF has not been used to monitor depth of anaesthesia in routine clinical practice. In this study, we have determined threshold values, sensitivity and specificity of the SEF that indicate intraoperative movements during general anaesthesia with isoflurane or propofol.

Patients and methods

After obtained Institutional Ethics Committee approval and informed consent, we studied 47 patients, aged 21–79 yr, ASA grades I and II, undergoing elective gynaecological or urological laparotomy. After oral premedication with a benzodiazepine (clorazepate dipotassium 20 mg) 45–60 min before anaesthesia, continuous electrocardiograph electrodes (ECG) and an i.v. catheter were inserted, and a continuous extradural block was performed at L3–4 or L4–5. Using 0.5% bupivacaine, the anaesthetic level was maintained at T4–5. Patients were allocated randomly to one of two groups (group 1, $n = 23$; group 2, $n = 24$). I.v. general anaesthesia was induced in group 1 with thiopentone 5 mg kg^{-1} and in group 2 with propofol 2 mg kg^{-1}. After induction of general anaesthesia and loss of consciousness (no response to verbal commands, loss of eyelid reflex), the patient's lungs were ventilated with 100% oxygen via a face mask. Vecuronium 0.1 mg kg^{-1} was given for neuromuscular block, the trachea was intubated and the lungs ventilated with 50% nitrous oxide in oxygen. No other neuromuscular blockers were used. To maintain general anaesthesia, patients in group 1 received 0.4–1.2 vol% isoflurane and patients in group 2 propofol 3–5 mg kg^{-1} h^{-1} i.v. End-expiratory concentrations of isoflurane were monitored continuously with a multi-gas analyser (Capnomac Ultima, Datex Instrument Corporation, Helsinki, Finland). Heart rate (by a three-lead ECG), systemic arterial pressure (by an arterial cannula in the radial artery) and central venous pressure (by a central venous catheter in the internal jugular vein)

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were recorded continuously. Mean arterial pressure was maintained greater than 70 mm Hg. Body core temperature was measured by an oesophageal temperature probe and maintained greater than 35.5 °C using heated blankets and warmed infusions. Controlled ventilation was adjusted to maintain normocapnia (end-expiratory carbon dioxide concentration 4.8–5.3 kPa) and verified by intermittent arterial blood-gas analysis. Individual doses of anaesthetics were guided by clinical signs of adequate anaesthesia, that is changes in arterial pressure, heart rate, sweating and tear production. Light anaesthesia was indicated by the "pressure rate, sweating and tears" (PRST) score [15]. A PRST score greater than 2 or spontaneous movements of the patients was defined as indicative of light anaesthesia. Spontaneous purposeful movements of the head and limbs, eye-opening or other facial movements were documented. Whenever movements occurred, the dose of the anaesthetic was increased to induce a clinically adequate level of anaesthesia. To evaluate conscious recall of anaesthesia and surgery, the patients were asked after operation to remember explicitly anything perceived during anaesthesia.

To obtain two-channel recordings of the EEG, silver electrodes were placed at C3/C4 (positive) and mastoids on both sides A1/A2 (negative) against the forehead as common electrode (FPZ), according to the international 10-20 system. The impedance of all electrodes was maintained less than 3000 Ω. A Cerebotrac 2500 (SRD Medical Ltd, Shorashim, Israel) was used to record, analyse and store the EEG signal. Bandpass filters were set at 1.5–30 Hz and amplifier sensitivity was 200 μV. The automatic artefact rejection was active and line current frequency suppression was set at 50 Hz. On-line power spectral analysis was performed using fast Fourier transformation (FFT). Epoch length of EEG acquisition was 4 s. Power spectrum was displayed as density spectral array. Spectral edge frequency 90 (SEF 90 = the frequency below which 90% of the EEG power is located) was calculated. Spectral bands of 0–4 Hz (delta) 4–8 Hz (theta), 8–13 Hz (alpha) and 13–30 Hz (beta) were analysed and the power of the spectral bands were calculated and expressed as percentage of total power. The delta ratio (ratio of power in the 8–30 Hz band to power in the 0–4 Hz band) was calculated. For off-line analysis, data were stored on a notebook computer (Compaq Ltd 25, Compaq Computer GmbH, München, Germany). Values for each of the derived variables were determined by averaging the data from 30 consecutive epochs. Where the value for an individual epoch was more than 2 SD from the mean it was omitted and replaced by an additional epoch. The EEG was recorded continuously on-line awake and during induction and maintenance of general anaesthesia until the end of anaesthesia, when the patients were extubated and had recovered from anaesthesia.

Results are presented as mean (SD). Cardiovascular variables and spontaneous movements were correlated by a time series analysis. For SEF 90 and the power bands beta, alpha, theta, delta and the delta ratio, the Wilcoxon test was used. Sensitivity (number of correctly predicted movements/total number of movements), specificity (number of correctly predicted situations of adequate anaesthesia/total number of situations of adequate anaesthesia) were calculated. Statistical significance was assumed if $P < 0.05$ after Bonferroni's correction for multiple comparisons.

Results

The two groups were comparable in age, sex distribution, weight, height, ASA physical status, type and dose of premedication, type of surgery, total time of surgery and anaesthesia, and total dose of bupivacaine (table 1).

Systolic (SAP) and diastolic (DAP) arterial pressure and heart rate (HR) awake, during maintenance of anaesthesia and during emergence from anaesthesia are presented in table 2. There was no significant change in heart rate. SAP and DAP decreased slightly during maintenance of anaesthesia and returned to awake baseline values at the end of anaesthesia in both groups. Sixteen movements in group 1 and 20 movements in group 2 were observed during maintenance of anaesthesia. All patients in each group moved spontaneously during emergence from anaesthesia shortly before tracheal extubation. The trachea of all patients was extubated and the patient had regained consciousness during the study at the end of anaesthesia. There was no correlation between haemodynamic data and movements, in the intraoperative period or during emergence from anaesthesia. At the postoperative interview no patient had explicit recall of intraoperative events.

Figure 1 shows the typical course of the power spectrum displayed as density spectral array and the spectral edge frequency awake, during induction and maintenance of general anaesthesia with isoflurane (fig. 1A) and propofol (fig. 1B), and during emergence from anaesthesia. With induction of general anaesthesia and during adequate general anaesthesia (no movement), in both patients SEF decreased from the awake baseline value of 18–20 Hz to 12–14 Hz. When a movement occurred during anaesthesia, SEF increased to the awake baseline value of 18–20 Hz. Deepening of general anaesthesia caused a decrease in SEF of 12–14 Hz. During emergence from general anaesthesia, SEF increased and at the end of anaesthesia shortly before extubation it returned to the awake baseline value of 18–20 Hz.

Mean SEF (Hz), total power (μV^2) and relative power in the frequency bands, delta, theta, alpha, beta and the delta ratio ($\alpha + \beta/\delta$) of the isoflurane and propofol groups awake, during maintenance of adequate general anaesthesia (no movement), before and during intraoperative spontaneous movements and during emergence from general anaesthesia are shown in table 3. Changes in SEF and the power bands were similar in both groups. Adequate anaesthesia caused a statistically significant decrease in SEF. Before and during intraoperative spontaneous movements in both groups there was a statistically significant increase in SEF compared with the state of adequate anaesthesia. The same was

Table 1 Patient data (mean (SD or range) or number)

	Group 1 (isoflurane)	Group 2 (propofol)
n	23	24
Age (yr)	54.02 (27–79)	53.89 (21–77)
Sex (m/f)	16/7	16/8
Weight (kg)	72.43 (9.13)	73.89 (13.91)
Height (cm)	169.06 (6.92)	167.06 (7.72)
ASA physical status	1.27 (0.47)	1.31 (0.55)
Type of surgery (*n*)		
Tumour nephrectomy	4	6
Abdominal hysterectomy	6	5
Radical hysterectomy	1	1
Lymphadenectomy	1	2
Exploratory laparatomy	11	10
Premedication		
Clorazepate dipotassium (mg/kg body weight)	0.34 (0.18)	0.27 (0.19)
Total dose of bupivacaine (mg/kg body weight)	2.07 (1.13)	1.82 (1.45)
Total duration of surgery (min)	165.38 (56.79)	179.60 (83.08)
Total duration of anaesthesia (min)	256.39 (78.21)	269.26 (86.31)

Table 2 Haemodynamic data (mean (SD)). HR = Heart rate, SAP = systolic arterial blood pressure, DAP = diastolic arterial blood pressure. *$P = 0.05$ compared with awake

	HR (beat min^{-1})	SAP (mm Hg)	DAP (mm Hg)
Group 1 (isoflurane)			
Awake	73.67 (13.69)	126.67 (19.38)	73.29 (10.92)
Anaesthesia (no movements)	68.94 (13.13)	115.99 (13.31)*	65.79 (10.44)*
Anaesthesia (movement)	77.92 (15.96)	130.92 (23.94)	69.29 (15.68)
Extubation	79.63 (15.71)	133.95 (26.95)	73.05 (17.61)
Group 2 (propofol)			
Awake	75.43 (13.68)	135.66 (20.74)	75.28 (9.42)
Anaesthesia (no movements)	68.41 (10.39)	117.43 (28.63)*	69.20 (13.16)*
Anaesthesia (movement)	69.97 (13.11)	125.78 (17.08)	67.97 (13.23)
Extubation	73.15 (13.31)	133.70 (19.79)	70.95 (13.43)

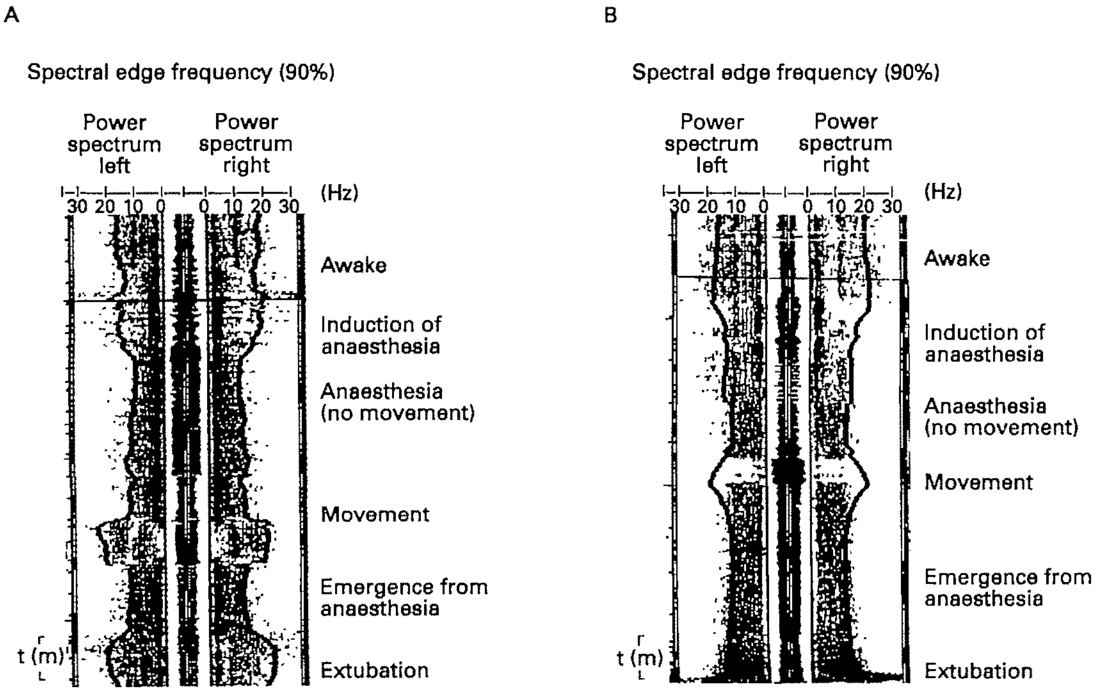

Figure 1 Typical course of the power spectrum displayed as density spectral array and the spectral edge frequency awake, during induction and maintenance of general anaesthesia with isoflurane (A) and propofol (B), and during emergence from anaesthesia.

seen during emergence from general anaesthesia (statistically significant increase in SEF). Relative power in the beta band decreased during adequate anaesthesia and increased during intraoperative spontaneous movements and during emergence from general anaesthesia. Relative power in the theta band

Table 3 Mean (SD) SEF (Hz), total power (μV), relative power in the frequency bands, δ, τ, α, β and the delta ratio, awake and during anaesthesia. *$P = 0.05$ compared with awake; †$P = 0.05$ compared with adequate anaesthesia

	SEF (Hz)	Total power (μV)	δ band (%)	τ band (%)	α band (%)	β band (%)	Delta ratio
Group 1 (isoflurane)							
Awake	16.14 (3.94)	55.38 (17.95)	34.51 (13.35)	17.75 (3.46)	26.18 (10.90)	21.57 (6.95)	2.25 (2.67)
Maintenance of anaesth.							
Anaesthesia (no movements)	12.46 (1.89)*	74.84 (30.91)*	33.03 (7.42)	22.42 (2.83)*	28.27 (6.07)	16.28 (4.48)*	1.68 (1.41)
8 min before movement	13.32 (2.11)	66.95 (20.92)*	30.63 (9.80)	22.38 (3.25)	28.72 (6.64)	18.27 (5.06)	2.14 (1.92)
6 min before movement	13.31 (2.47)	65.94 (20.23)	29.44 (9.63)	23.53 (3.33)*	28.80 (6.66)	18.23 (6.30)	2.55 (2.25)
4 min before movement	14.01 (2.49)	71.79 (42.62)	28.20 (9.78)	20.70 (3.55)*	28.99 (7.49)	19.11 (5.36)	2.82 (2.44)
2 min before movement	13.91 (3.00)	66.79 (38.93)	28.59 (10.14)	20.30 (4.86)*	27.88 (7.46)	20.23 (6.54)†	2.76 (2.49)
Movement	17.42 (4.06)*†	68.04 (36.64)	26.50 (12.67)†	18.51 (7.24)†	26.00 (5.57)	25.99 (9.45)†	3.10 (3.86)
Emergence from anaesth.							
8 min before movement	13.42 (1.98)*	68.59 (22.98)*	28.56 (8.59)	22.71 (3.28)*	30.24 (7.28)	18.49 (4.72)	2.44 (2.22)
6 min before movement	14.73 (3.11)	64.56 (19.72)*	27.95 (8.76)	23.05 (4.19)*	28.38 (8.04)	20.62 (6.16)†	3.15 (4.53)
4 min before movement	15.26 (2.91)†	71.41 (38.10)*	26.12 (8.01)†	23.58 (4.19)*	29.12 (6.88)	21.17 (6.00)†	3.07 (2.58)
2 min before movement	16.26 (4.12)†	68.72 (35.26)†	24.98 (7.87)†	21.59 (5.59)	28.21 (5.92)	25.22 (9.09)†	4.18 (4.43)
Extubation	18.90 (3.88)†	66.48 (33.97)*	27.97 (10.19)†	18.47 (6.52)†	24.39 (8.33)	26.17 (6.59)†	2.63 (2.48)
Group 2 (propofol)							
Awake	14.04 (3.21)	70.95 (14.71)	34.11 (14.01)	16.63 (3.24)	28.34 (14.66)	20.92 (5.44)	2.49 (3.83)
Maintenance of anaesth.							
Anaesthesia (no movements)	11.89 (1.28)*	85.52 (20.63)*	34.08 (5.08)	22.01 (3.89)*	29.12 (5.65)	14.78 (2.85)*	1.28 (0.86)
8 min before movement	12.91 (2.22)	89.57 (13.48)*	29.62 (6.09)	22.02 (4.15)*	30.21 (6.73)	18.15 (7.51)	1.91 (1.68)
6 min before movement	12.92 (1.88)	91.43 (13.70)*	29.51 (5.92)	21.92 (4.89)*	31.03 (6.48)	17.54 (6.27)	1.51 (1.22)
4 min before movement	13.61 (2.94)†	89.69 (14.18)*	28.48 (7.86)	20.81 (5.07)*	30.11 (6.24)	20.60 (10.60)†	1.80 (1.55)
2 min before movement	15.04 (3.05)†	89.31 (13.28)*	25.71 (7.83)*†	20.22 (5.37)†	29.06 (5.92)	25.01 (10.83)*†	2.90 (4.50)
Movement	18.08 (3.72)*†	89.79 (16.17)*	24.84 (10.68)†	18.02 (3.57)†	25.94 (6.00)	31.20 (11.42)*†	3.78 (5.32)
Emergence from anaesth.							
8 min before movement	14.02 (3.55)	87.88 (16.48)*	27.90 (6.71)	21.47 (4.46)*†	30.99 (5.51)	19.64 (8.72)†	3.96 (6.74)
6 min before movement	14.40 (3.74)	89.49 (13.61)*	27.15 (7.31)†	21.94 (4.46)*†	30.07 (4.90)	20.85 (9.49)†	3.80 (5.82)
4 min before movement	14.88 (3.71)†	90.15 (11.91)*	27.95 (7.76)	20.81 (4.25)*†	29.08 (5.00)	22.15 (9.33)†	3.28 (4.01)
2 min before movement	15.67 (3.55)†	92.92 (15.10)*	28.34 (8.61)†	20.17 (4.47)*†	28.04 (5.84)	23.44 (7.50)†	2.82 (2.41)
Extubation	18.30 (4.34)†	85.73 (15.43)*	26.04 (7.43)†	19.34 (4.86)†	23.70 (4.23)	29.92 (8.52)*†	4.14 (4.97)

Table 4 Threshold values of EEG variables for movements during anaesthesia

	Threshold value	Sensitivity (%)	Specificity (%)
Group 1 (isoflurane)			
SEF (Hz)	14	73.33	76.26
Total power (μV)	100	95.00	17.09
δ band (%)	40	81.67	18.18
τ band (%)	20	53.33	73.23
α band (%)	30	15.00	57.87
β band (%)	30	21.67	95.98
Delta ratio	3.0	25.81	83.33
Group 2 (propofol)			
SEF (Hz)	14	70.67	88.24
Total power (μV)	100	82.67	30.33
δ band (%)	40	74.67	21.80
τ band (%)	20	72.00	61.24
α band (%)	30	25.68	59.72
β band (%)	30	28.00	98.58
Delta ratio	3.0	34.25	93.33
Groups 1+2			
SEF (Hz)	14	71.85	82.34
Total power (μV)	100	88.15	23.90
δ band (%)	40	77.78	20.05
τ band (%)	20	63.70	67.08
α band (%)	30	20.90	58.82
β band (%)	30	25.19	97.32
Delta ratio	3.0	30.37	88.48

increased during adequate anaesthesia and decreased during intraoperative movements and emergence from anaesthesia in both groups. Relative power in the delta and alpha bands and the delta ratio did not change significantly during anaesthesia.

In table 4 are shown threshold values for SEF and the relative power in the delta, theta, alpha and beta bands, with their calculated sensitivities and specificities within and between groups to separate adequate anaesthesia (no movement) from intraoperative spontaneous movements. SEF of 14 Hz provided a sensitivity of 73% and a specificity of 76% in the isoflurane group, and a sensitivity of 70% and a specificity of 88% in the propofol group. Between groups a threshold value of SEF 14 Hz had a sensitivity of 72% and a specificity of 82% to separate adequate anaesthesia (no movement) from intraoperative spontaneous movements.

Discussion

There was no correlation in our study between physiological signs of wakefulness (increase in heart rate and arterial pressure) and motor signs of wakefulness during a combination of extradural analgesia with bupivacaine and general anaesthesia with isoflurane or propofol. This observation may be explained by the extensive extradural block in all patients during surgery. It interfered with the cardiovascular variables by attenuating arterial pressure responses by sympathetic block. In this study we combined regional and general anaesthesia to minimize the effect of pain on the level of arousal. Furthermore, extensive spinal block was thought to inhibit reflex movements in response to pain, as intended by the spinal cord. This should facilitate the interpretation of patient movement, as intended by the cortex.

SEF decreased during general anaesthesia with isoflurane or propofol compared with the awake state. During intraoperative spontaneous movements and emergence from anaesthesia with isoflurane or propofol, SEF increased to near awake baseline values. Nevertheless, because of the range of overlap of SEF during adequate anaesthesia (no movement) and intraoperative spontaneous movements, sensitivity and specificity were only 70–88% within and between groups.

Schwilden, Schüttler and Stoeckel used the median frequency of the EEG in volunteers to define depth of anaesthesia and to develop pharmacokinetic–pharmacodynamic models during i.v. anaesthesia. They found, during a threefold repetitive infusion of etomidate in volunteers, a correlation between median frequency and serum concentrations of the i.v. anaesthetic [8]. With increasing serum concentrations of etomidate, median frequency decreased from the awake baseline value of about 9 Hz to the anaesthetic value of approximately 2 Hz. With decreasing blood concentrations of etomidate, median frequency increased and returned to the awake value of approximately 8 Hz. A similar relation between median frequency and blood concentrations of i.v. anaesthetics was observed by Schwilden, Schüttler and Stoeckel [9] and Schüttler and colleagues during anaesthesia with methohexitone, propofol and ketamine [11, 16]. The awake median frequency in their studies was approximately 9 Hz, loss of consciousness occurred at about 5 Hz, the corneal reflex was absent at approximately 2 Hz and a burst suppression pattern occurred at about 1.5 Hz. The burst suppression patterns disappeared at median frequencies of approximately 1.8 Hz, the corneal reflex returned at approximately 2 Hz, responsiveness returned at approximately 5 Hz and orientation occurred at approximately 6–7 Hz. In one study, concentrations of isoflurane and nitrous oxide of 1.3 and 1.5 MAC, respectively, were associated with an EEG median frequency of less than 5 Hz and adequate intraoperative anaesthesia

[10]. In this study median frequency was greater than 5 Hz, when subjects were conscious and responsive.

Drummond and co-workers studied the processed EEG during general anaesthesia with isoflurane and during emergence from anaesthesia [12]. Most patients showed an increase in median frequency and SEF immediately before arousal compared with anaesthesia. Nevertheless, because of the range of overlap between anaesthesia and arousal, the sensitivity and specificity of median frequency and SEF in predicting arousal during anaesthesia was low, as in this study. They concluded that none of the EEG descriptors can serve as a completely reliable predictor of imminent arousal during anaesthesia.

Dwyer and co-workers found that the EEG could not predict depth of isoflurane anaesthesia [17]. They found that EEG activity and SEF decreased dose-dependently during anaesthesia with isoflurane. Nevertheless, the SEF of patients who moved purposefully in response to incision was 19.8 and did not differ from the SEF of 19.3 in patients who did not move. Memory of information presented during general anaesthesia did not correlate with values of any of the derived EEG variables. Response to commands in the intraoperative period was associated with lower anaesthetic concentrations of isoflurane, but there was no difference in the derived EEG variables between responders with an SEF of 22.1 and non-responders with an SEF of 21.3.

Unfortunately, there are no other clinical studies that have investigated the usefulness of the derived EEG variables, median frequency or SEF, in predicting intraoperative movements, arousal, awareness or memory formation for the commonly used anaesthetics. It seems that the typical clinical environment, in which multiple drugs are given and clinical end-points are not defined clearly, the success in determining depth of anaesthesia and predicting intraoperative movements and arousal with EEG variables is limited.

References

1. Clark DL, Rosner BS. Neurophysiologic effects of general anesthetics: I. The electroencephalogram and sensory evoked responses in human. *Anesthesiology* 1973; **38**: 564.
2. Levy WJ, Shapiro HM, Maruchak G, Meathe E. Automated EEG processing for intraoperative monitoring. *Anesthesiology* 1980; **53**: 223–236.
3. Levy WJ. Intraoperative EEG patterns: implications for EEG monitoring. *Anesthesiology* 1984; **60**: 430–434.
4. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985; **62**: 234–241.
5. Hudson RJ, Stanski DR, Saidman LJ, Meathe E. A model for studying depth of anesthesia and acute tolerance to thiopental. *Anesthesiology* 1983; **59**: 301–308.
6. Chi OZ, Sommer W, Jasaitis D. Power spectral analysis of EEG during sufentanil infusion in humans. *Canadian Journal of Anaesthesia* 1991; **38**: 275–280.
7. Smith NT, Dec-Silver H, Sanford TJ, Westover CJ, Quinn ML, Klein F, Davis DA. EEGs during high-dose fentanyl-, sufentanil-, or morphine–oxygen anesthesia. *Anesthesia and Analgesia* 1984; **63**: 386–393.
8. Schwilden H, Schüttler J, Stoeckel H. Quantitation of the EEG and pharmacodynamic modelling of hypnotic drugs: etomidate as an example. *European Journal of Anaesthesia* 1985; **2**: 121–131.
9. Schwilden H, Schüttler J, Stoeckel H. Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. *Anesthesiology* 1987; **67**: 341–347.
10. Schwilden H, Stoeckel H. Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. *British Journal of Anaesthesia* 1987; **59**: 738–745.
11. Schüttler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, Sheiner LB. Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in human. *Journal of Pharmacokinetics and Biopharmaceutics* 1987; **15**: 241.
12. Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anaesthesia. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 693–699.
13. Rampil IJ, Sasse FJ, Smith NT, Hoff BH, Flemming DC. Spectral edge frequency—a new correlate of anesthetic depth. *Anesthesiology* 1980; **53**: 512–517.
14. Schwilden H. Use of the median EEG frequency and pharmacokinetics in determining depth of anaesthesia. In: Jones JG, ed. *Clinical Anaesthesiology vol. 3/Nr. 3*. London: Bailliere Tindall, 1989; 603–623.
15. Evans JM. Clinical signs and autonomic responses. In: Rosen M, Lunn JN, eds. *Consciousness, Awareness and Pain in General Anaesthesia*. London: Butterworths, 1987; 18–34.
16. Schüttler J, Schwilden H, Stoeckel H. Pharmacokinetic and pharmacodynamic modelling of propofol ('diprivan') in volunteers and surgical patients. *Postgraduate Medical Journal* 1985; **61**(Suppl. 3): 53–54.
17. Dwyer R, Rampil IJ, Eger EI II, Bennett HL. The electroencephalogram does not predict depth of isoflurane anesthesia. *Anesthesiology* 1994; **81**: 403–409.

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The reinforced laryngeal mask airway for dento–alveolar surgery

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Summary

We have evaluated the reinforced laryngeal mask airway (LMA) for use during dento–alveolar surgery in 100 ASA I and II day-case patients allocated randomly to receive either a nasotracheal tube or reinforced LMA. We recorded ease of airway insertion, airway complications, quality of recovery and replies to a 24-h postoperative questionnaire. In addition, a fibreoptic assessment was made of laryngotracheal soiling, and the effect of head movement and the position of the reinforced LMA. There were no significant differences in difficulty in airway positioning or perioperative oxygen desaturation. Nineteen patients in the nasotracheal tube group had epistaxis ($P = 0.001$) and laryngotracheal soiling occurred in three of these patients. Two reinforced LMA were dislodged on moving into the operating theatre and in a further five patients in this group there was partial airway obstruction (compared with none in the nasotracheal tube group; $P = 0.018$) which was caused by downward pressure on the mandible by the surgeon. There were no differences in postoperative complications. No surgeon reported poor access to the operating field. Overall the reinforced LMA provided satisfactory conditions for this surgery but vigilance of the airway was required, especially at the time of extraction. (*Br. J. Anaesth.* 1996; **77**: 185–188)

Key words

Equipment, masks anaesthesia. Complications, airway obstruction. Surgery, dental.

Anaesthesia for oral surgery requires a technique which provides a stable, unobstructed airway and permits good surgical access with few complications. Recent studies on adenotonsillectomy procedures [1, 2] showed that the Brain reinforced laryngeal mask airway (LMA) provided a satisfactory airway and protection against soiling from the operation site. The reinforced LMA has potential for airway management during surgical exodontic procedures and although this is a commonly used technique [3, 4], a recent review [5] has highlighted the lack of standardized, randomized studies in this area. To our knowledge no study has been performed to quantify the problems in a standardized, controlled manner.

In this study, we assessed the following: maintenance of the airway, protection against soiling and any effects resulting from manipulation of the temporo–mandibular joint, and movement of the reinforced LMA, which are more pronounced in oral surgery.

Patients and methods

After obtaining local Ethics Committee approval and written, informed consent, we studied 100 consecutive ASA I and II patients undergoing day-case oral surgery (predominantly surgical extraction of wisdom teeth). Patients were allocated randomly to one of two groups: group A received the reinforced LMA and group B the plastic nasotracheal Mallinckrodt tube (size 7.0 in men and 6.5 in women). Patients were aged 18–60 yr with no pre-existing lung pathology. Exclusion criteria were contraindications to the use of the reinforced LMA, such as obesity and gastro–oesophageal reflux.

The reinforced LMA was inserted according to the manufacturer's recommended technique [3]. Most adults had a size 4, apart from females < 50 kg. In both groups anaesthesia was induced with propofol 1–2 mg kg^{-1} and fentanyl 1 µg kg^{-1}, and maintained with isoflurane and 70 % nitrous oxide in oxygen. In group A, patients breathed isoflurane and nitrous oxide in oxygen spontaneously via the reinforced LMA. In order to facilitate moving the tube to the other side of the mouth if bilateral procedures were being undertaken, the reinforced LMA was not taped in position. In group B, mivacurium 0.15 mg kg^{-1} was used to facilitate nasotracheal intubation and maintain paralysis for IPPV with isoflurane and nitrous oxide in oxygen. The nasopharynx was not treated with a vasoconstrictor before inserting the nasotracheal tube, however, the nasotracheal tubes were warmed before use. During the procedure all patients received ketorolac 10 and 20 mg i.v. for postoperative analgesia and a gauze pharyngeal pack was inserted in both groups.

The following were monitored throughout the procedure: ECG, non-invasive arterial pressure, oxygen saturation, inspired oxygen and end-tidal carbon dioxide concentration, and isoflurane concentrations. Airway pressure and neuromuscular function were monitored in patients in group B. The technical problems encountered with each airway were noted. These included difficult insertion, epistaxis, displacement of the reinforced LMA,

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repositioning and whether or not mandibular support was required to maintain airway patency at any point in the procedure.

After surgery we increased the inspired concentration of isoflurane to 3% in 100% oxygen, the larynx, trachea, or both, were inspected for soiling from blood or secretions, and the position of the reinforced LMA was checked. We used the Keymed fibreoptic laryngoscope and advanced it no further than just through the grill of the mask or past the tip of the nasotracheal tubes unless there was obvious airway soiling distally. In group A patients undergoing bilateral procedures, the airway was also examined after extractions on the first side in order to assess any effect of the surgeons moving to the contralateral side. At the end of surgery the pharyngeal pack was removed, the pharynx was cleared by suction and the patients emerged from anaesthesia and in the left lateral position, head down. In group A, the reinforced LMA was removed in recovery when the patients awoke; the dental packs on the extracted tooth sockets prevented biting on the mask. In group B patients, the trachea was extubated with the patient awake.

During recovery, the following variables were noted by the recovery staff: airway maintenance—easy, mandibular support or airway required, airway conditions—good, coughing, biting, laryngeal spasm, suction—easy/difficult/not required, and desaturation < 95%. After the procedure the anaesthetist and surgeon were asked to grade the quality of the airway and surgical access, respectively, as excellent, good, fair or poor.

Before the patients left the institute they were given a questionnaire to complete 24 h after operation, and their replies obtained by telephone from one of the investigators (A. C. Q., A. S.).

Data were analysed using SPSS v6 for Windows statistical package. Chi-square and t tests were used as appropriate. Significance was considered at $P < 0.05$.

Results

In total, 100 consecutive patients were recruited to the study, 50 in the reinforced LMA group (group A) and 50 in the nasotracheal group (group B). There were no significant differences in patient data between the groups (table 1), and there were more females than males.

Table 1 Patient data (mean (range) or number). No significant differences between groups

Total ($n = 100$)	Reinforced ($n = 50$)	Nasotracheal tube ($n = 50$)
Age (yr)	26 (19–42)	26 (17–60)
Sex (M/F)	15/35	Male = 20/30
Teeth extracted	2.5 (1–4)	2.8 (1–4)

There were no significant differences in the incidence of difficulties with positioning of the airway, but in group A, two patients required repositioning of the reinforced LMA which was dislodged in transit from the anaesthetic room to theatre (table 2). There was a significantly greater incidence of epistaxis in the nasotracheal tube group (19 compared with 0; $P = 0.001$) and a higher incidence of partial obstruction in the reinforced LMA group (five compared with no cases: $P = 0.018$).

On fibreoptic examination of the airway during reinforced LMA anaesthesia, we found that in 25 cases the epiglottis was positioned outside the mask and in 33 cases the reinforced LMA was positioned centrally over the larynx. There was no laryngotracheal soiling with blood or debris in group A. Fibreoptic examination of the nasotracheal tube group showed that there were three cases of tracheal soiling with blood, all associated with epistaxis after passage of the tube. Soiling consisted of small spots of blood in the trachea below the tube, but there was no evidence of obstruction. One patient in group B developed bronchospasm after induction resulting in mildly increased airway pressures, which stabilized spontaneously during maintenance with isoflurane.

Desaturation did not occur in either group before or during operation, but in the recovery period saturation occurred most often in group B (six compared with two; ns). Desaturation was transient and Sa_{O_2} did not decrease to less than 90% with supplementary oxygen 4 litre min^{-1}. After operation there were no other problems with airway management, but the recovery staff reported a qualitatively superior recovery with the reinforced LMA.

There was an 88% reply rate to the questionnaire which was distributed evenly between the groups (table 3). There was no significant difference between the groups in the incidence or severity of postoperative headache, nausea, vomiting, sore throat, thirst, jaw pain, hoarseness or preoperative anxiety. Overall there was a low incidence of nausea (75% experienced no nausea) together with a very low incidence of vomiting (5.7%). After operation, sore throat occurred in 58.9% of patients which was mostly of a mild nature. The majority (60–70%) of patients experienced moderate or severe jaw pain after operation.

Comparing overall satisfaction with the airways, anaesthetists felt that both tubes provided an excellent airway in the majority of patients (group B,

Table 2 Intraoperative observations. *Dislodged in transit from anaesthetic room to theatre

	Reinforced LMA ($n = 50$)	Nasotracheal tube ($n = 50$)	P
Epistaxis	0	19	0.001
Difficult to position	5	3	ns
Partial obstruction	5	0	0.018
Repositioning*	2	0	ns
Desaturation in the recovery period	2	6	ns

Table 3 Replies to the postoperative questionnaire (88 % reply rate). No significant differences between groups

	Reinforced LMA ($n = 50$)	Nasotracheal tube ($n = 50$)
Sore throat		
Nil	18	20
Mild	15	18
Moderate	9	4
Severe	4	4
Headache	19	12
Nausea	9	13
Vomiting	2	3
Jaw pain (moderate/severe)	35	30

Table 4 Overall satisfaction with each airway

Airway	Rating	Anaesthetist
Reinforced LMA	Excellent	42
($n = 50$)	Good	3
	Fair	5
Nasotracheal tube	Excellent	49
($n = 50$)	Good	1
	Fair	0
Access		Surgeon
Reinforced LMA	Excellent	43
($n = 50$)	Good	5
	Fair	2
Nasotracheal tube	Excellent	50
($n = 50$)	Good	0
	Fair	0

49 compared with group A, 42) (table 4). The reinforced LMA provided only a fair airway in five patients which accounts for the cases of partial obstruction. On no occasion was either airway described as poor. Surgical satisfaction with access was noted as excellent in the majority of patients (group B, 50 compared with group A, 43); none considered access poor in any case.

Discussion

The purpose of this study was to assess conditions provided by the reinforced LMA during oral surgery compared with nasotracheal intubation. Although we are aware of its widespread use in this area, we felt it was important to fully study the advantages and disadvantages of the technique and confirm its safety. The use of the LMA in various oral surgical procedures has been studied extensively but the following features have not been elucidated fully: inspection of the position of the mask and obstruction of the airway, and perioperative problems, including airway access, postoperative sore throat and nausea and vomiting, compared with nasotracheal intubation. Our results showed that the reinforced LMA may be used safely in place of nasotracheal intubation during anaesthesia for extraction of wisdom teeth. The mask provided a clear and effective airway in 90 % of cases until emergence from anaesthesia and also provided good surgical access. It is worth noting that this study was carried out at a University Dental Institute where many inexperienced trainee oral surgeons were performing the extractions but who coped well with the reinforced LMA in the oral cavity.

We inserted the reinforced LMA according to the manufacturer's instruction but initially found the technique moderately difficult, presumably because of lack of experience with the technique. A recent article examining 1500 LMA insertions by a single anaesthetist [6] illustrates this learning curve—there was an improvement in the author's technique after the first 750 insertions. The reinforced LMA was not taped to the face during bilateral procedures to enable the surgeon to move the tubing of the reinforced LMA if access was poor or on changing operating sides (it was more troublesome to attempt to remove tape under the surgical drapes halfway through the procedure). No repositioning of the reinforced LMA was required as a result of obstruction during operation. The need for repositioning on two occasions occurred on transit from the anaesthetic room to theatre where the mask was accidently pulled out. Both masks were repositioned easily before commencing surgery.

In the five reinforced LMA cases in which partial obstruction occurred, this was caused during downward pressure on the mandible as the forceps were applied round the tooth to remove it from its socket. Unfortunately we were unable to assess the position of the reinforced LMA at that point although we can speculate that it may have been pushed up more against the proximal anterior laryngeal wall. All obstructions were corrected by counter pressure on the mandible. Overall the rate of obstruction was similar to that found previously [7–9] but there was no correlation with the position of the reinforced LMA over the cords with respect to the epiglottis and the incidence of obstruction.

Interestingly three cases in the nasotracheal tube group were difficult to position, indicating that the standard technique was not without problems. Also, there was a high incidence (38 %) of epistaxis and the only three cases of laryngotracheal soiling occurred in this group. However, we did not pretreat the nasopharynx with a vasoconstrictor.

We were surprised that in the reinforced LMA group there was a high incidence of severe or moderate sore throat compared with the nasotracheal tube group, contrary to previous findings [10]. In part this may have reflected our inexperience with the reinforced LMA (proportionately more sore throats early in the study) but it is more likely to be caused by a gauze dental pack in the pharynx. We deliberated on whether or not the pack was necessary as it has the potential to displace the reinforced LMA leading to obstruction and may be superfluous as the LMA affords excellent airway protection from secretions from above (but not below) [11]. However, given the degree of soiling of some of the packs we preferred to use them and so minimize blood-/secretions entering the stomach. This may be reflected in the low incidence of postoperative nausea and vomiting given the young age of the patients, the high proportion of females, the type of surgery and the fact that no antiemetics were prescribed.

References

1. Williams PJ, Bailey PM. Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy. *British Journal of Anaesthesia* 1993; **70**: 30–33.
2. Webster AC, Morley, Forster PK, Ganapathy S, Ruby R, Au A, Cook MJ. Anaesthesia for adenotonsillectomy; a comparison between tracheal intubation and the armoured laryngeal mask airway. *Canadian Journal of Anaesthesia* 1993; **40**: 1171–1177.
3. Alexander CA. A modified Intravent laryngeal mask airway for ENT and dental surgery. *Anaesthesia* 1990; **45**: 892–893.
4. Leach AB, Alexander CA. The laryngeal mask—an overview. *European Journal of Anaesthesiology* 1991; **54**: 19–31.
5. Brimacombe J, Berry A. The laryngeal mask airway for dental surgery—a review. *Australian Dental Journal* 1995; **40**: 10–14.
6. Brimacombe J. Analysis of 1500 laryngeal mask uses by one anaesthetist in adults undergoing routine anaesthesia. *Anaesthesia* 1996; **51**: 76–80.
7. Nandi PR, Nunn JF, Charlesworth, Taylor SJ. Radiological study of the laryngeal mask. *British Journal of Anaesthesia* 1991; **66**: 157–162.
8. Payne J. The use of the fibreoptic laryngoscope to confirm the position of the laryngeal mask. *Anaesthesia* 1989; **44**: 865.
9. Rowbottom SJ, Simpson DL. Partial obstruction of the laryngeal mask airway. *Anaesthesia* 1990; **45**: 892.
10. Alexander CA, Leach AB. Incidence of sore throats with the laryngeal mask. *Anaesthesia* 1989; **44**: 791.
11. Johns RE, Hill S, Hughes TJ. Airway protection by the laryngeal mask. *Anaesthesia* 1991; **46**: 366–367.

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Isoflurane waste gas exposure during general anaesthesia: the laryngeal mask compared with tracheal intubation

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Summary

We have compared exposure to isoflurane while using the laryngeal mask airway (LMA) during anaesthesia under positive pressure ventilation with exposure while using tracheal intubation. Trace concentrations of isoflurane were measured directly using a highly sensitive photoacoustic infrared spectrometer (Bruel and Kjaer 1302, Denmark) during general anaesthesia in 20 eye surgery procedures. Measurements were made at six locations (three personnel-related, three leakage-related) in the operating theatre. Despite some high isoflurane values (greater than 2000 ppm at one leakage-related measurement point) all measured values at the personnel-related points were low (the majority were less than isoflurane 2 ppm). In the LMA group, mean trace concentrations were slightly higher than in the tracheal tube (ET) group. Mean exposure to isoflurane, expressed as median (range) related to anaesthetic administration, was highest for the auxiliary nurse (0.64 (0.22–26.89) ppm for the LMA compared with 0.31 (0.02–1.07) ppm for the tracheal tube), followed by the anaesthetist (0.50 (0.28–2.28) ppm for the LMA compared with 0.35 (0.02–0.73) ppm for the tracheal tube) and the surgeon (0.36 (0.20–3.93) ppm for the LMA compared with 0.29 (0.01–0.50) ppm for the tracheal tube). We conclude that the use of the LMA in patients undergoing ventilation is not associated necessarily with high concentrations of isoflurane in a modern working environment (*Br. J. Anaesth.* 1996; **77**: 189–193)

Key words

Anaesthetics volatile, isoflurane. Anaesthesia, general. Equipment, masks anaesthesia. Intubation tracheal.

American and most European public health authorities recommend threshold values (table 1) for occupational exposure to trace concentrations of volatile anaesthetic agents. The National Institute for Occupational Safety and Health (NIOSH) recommends that occupational exposure to halogenated anaesthetic agents, when used as the sole anaesthetic, should not exceed 2 ppm, expressed as time-weighted averages (TWA) [1]. In European countries, recommended threshold values for these agents range from 2 to 20 ppm. Most of the national exposure standards are related to an 8-h TWA, although the NIOSH values relate to TWA over the period of anaesthetic administration.

The laryngeal mask airway (LMA) is a relatively new device for management of the airway during general anaesthesia [2]. Brain and colleagues stated that the LMA was gas-tight in positive pressure ventilation up to 30 cm H_2O [3]. A recent study has shown mean leak values of up to 27% of the inspired volume during LMA use and up to 4% during tracheal intubation, both under positive pressure ventilation (IPPV) [4]. Such high leakage during laryngeal mask anaesthesia could result in pollution of the operating theatre.

To date, data on occupational exposure of operating theatre personnel to theatre pollution during LMA anaesthesia have been available only for nitrous oxide. Lambert-Jensen, Christensen and Brynnum reported nitrous oxide exposure, comparing spontaneous and controlled ventilation using the LMA [5], and Sarma and Leman reported low nitrous oxide concentrations during spontaneous breathing [6].

In this study we measured exposure to isoflurane while using the LMA during anaesthesia with IPPV in an operating theatre with air conditioning and scavenging systems conforming to NIOSH recommendations, and compared these concentrations with exposure while using tracheal intubation under identical conditions. In contrast with earlier studies, staff exposure (surgeon, anaesthetist and auxiliary nurse) was recorded directly at the subject's mouth, and three static points (operation area, mouth of the patient and reservoir bag of the anaesthesia machine) related to potential leakage sources were also measured.

Methods and materials

STUDY POPULATION

We studied 20 patients undergoing ophthalmological procedures under general anaesthesia in a prospective, randomized study. The treatment assignments (tracheal tube or LMA) were contained in sequen-

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Table 1 International threshold values. Current threshold values as time-weighted averages (TWA) in parts per million (ppm). NIOSH values refer to the time of exposure during anaesthetic administration, all other countries refer to an 8-h-workday TWA. * (Combination of nitrous oxide (N_2O) and halogenated agents reduces the threshold value to 0.5 ppm for the halogenated agents)

	N_2O	Halothane	Enflurane	Isoflurane
Denmark	100	5	2	—
France	—	2	—	—
Germany	100	5	20	—
Italy	100	—	—	—
Norway	100	5	2	2
Sweden	100	5	10	10
Switzerland	—	5	—	—
USA-NIOSH*	25	2	2	2
USA-ACGIH	50	50	75	—
UK	100	10	50	50

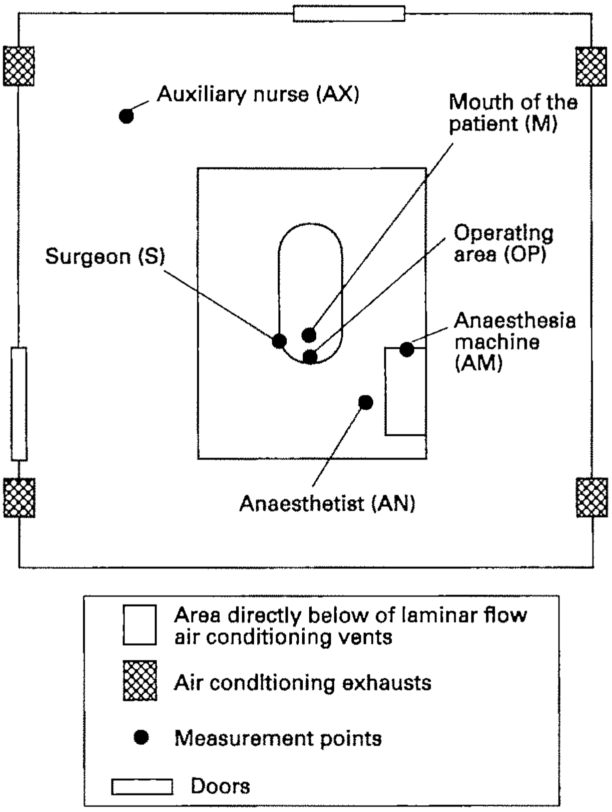

Figure 1 Ground plan of the operating theatre and locations of the measurement points.

tially ordered sealed envelopes, which were opened before induction of anaesthesia. Ten patients received an LMA (group 1) and 10 patients a tracheal tube (ET = group 2). The study did not influence routine patient management. Induction, maintenance and emergence from anaesthesia were performed in the operating theatre. Anaesthesia was induced with propofol 1.5–3.0 mg kg^{-1} (until loss of eyelash reflex) and maintained with i.v. alfentanil and isoflurane, and 65% air in oxygen. Administration of isoflurane as the sole volatile anaesthetic agent was started after insertion of either the LMA or tracheal tube. A size 4 laryngeal mask was inserted by one of two anaesthetists using the technique recommended by the manufacturer. Tracheal RAE tubes (Mallinckrodt Medical, Germany) with an internal diameter of 7.5 mm or 7.0 mm were used for male and female patients, respectively. Fresh gas flow was 4 litre min^{-1}. A new low-leakage [7] Sulla 808 V (Draeger, Germany) was used as the anaesthesia machine. Inspiratory isoflurane concentration and ventilation pressures were recorded using a Capnomac infrared analyser (Datex, Finland). The waste gas outlets of both the anaesthesia machine and the infrared analyser were connected to the central scavenging system (60 litre min^{-1}) of the hospital.

WORKPLACE DESCRIPTION

The air volume of the operating theatre in this study was 130 m^3. Ventilation and air conditioning systems were separate from those serving other rooms of the hospital. Connections between the recovery room, other operating theatres and the operating theatre of the study did not exist. Air conditioning was performed by a laminar flow system producing an air change rate of 20 changes per hour (2600 $m^3 h^{-1}$) without recirculation. The location of the area below the air conditioning vents is shown in figure 1.

SAMPLING STRATEGY

Trace concentrations of isoflurane were measured directly using a highly sensitive photoacoustic infrared spectrometer (Bruel and Kjaer 1302, Denmark). The lower detection limit for isoflurane was 0.009 ppm and accuracy was within ±2% of the measured value. Gas was sampled under ambient pressure conditions using 8-m lengths of polyamide tubes (Siegle, Germany). Air samples were obtained sequentially at six locations (fig. 1) in the operating theatre using a Bruel and Kjaer 1303 multipoint sampler. Three measurement points were personnel-related: AN = anaesthetist, S = surgeon, AX = auxiliary nurse. Sampling tubes were fitted at the operating theatre personnel's masks, and therefore air sampling was accomplished within the breathing zone. The other three sampling points were at the sites of potential leaks: OP = operation area, M = mouth of the patient, AM = reservoir bag of the anaesthesia machine. Data from the infrared spectrometer were recorded continuously using a personal computer system. Cuff pressure in the ET group was kept within the range of 20–30 cm H_2O using an Endotest (Ruesch, Germany) manometer.

MATHEMATICS

To calculate mean exposure during administration of anaesthetic, concentrations were calculated for each anaesthetic from the area under the curves derived from intermittent measurements. These mean trace concentrations for each anaesthetic and all locations are plotted in figure 2. Median and range were calculated for each location and group and presented in table 3. Between-locations and between-group comparisons were performed using the Wilcoxon test ($P < 0.05$).

Results

Both anaesthetists were experienced in inducing and maintaining general anaesthesia using the LMA or tracheal tube. The masks were introduced successfully on the first or second attempt.

Mean values for exposure time during anaesthesia, ventilation pressures, inspiratory isoflurane concentration and patient data were comparable in both groups (table 2). Median and ranges of mean trace concentrations of isoflurane in both groups are shown in table 3. Distributions of mean trace concentrations of the individual anaesthetic procedures are illustrated in figure 2.

Table 2 Patient data (mean (SD) or number)

	LMA group (n = 10)	ET group (n = 10)
Duration of anaesthesia (min)	72 (34)	79 (24)
Surgical procedure		
Cataract	9	7
Vitrectomy	1	2
Cerclage	0	1
Sex (M/F)	7/3	6/4
Ventilation pressures (cm H_2O)		
PEEP	4.1 (1.1)	4.2 (1.2)
Plateau	15.8 (2.4)	15.7 (3.5)
Peak	21.8 (2.8)	22.4 (4.9)
Inspiratory isoflurane concentration (vol %)	1.21 (0.25)	1.18 (0.24)

Table 3 Median (range) mean trace concentrations related to the time over the duration of anaesthetic administration at the different measurement points in the operating theatre. Values are in parts per million (ppm). Significant differences (P < 0.05): *within leakage-related values; †between groups

Location	LMA group	ET group
Personnel-related values		
Anaesthetist (AN)	0.50 (0.28–2.28)	0.35 (0.02–0.73)
Surgeon (S)	0.36 (0.20–3.93)	0.29 (0.01–0.50)
Auxiliary nurse (AX)	0.64 (0.22–26.89)	0.31 (0.02–1.07)
Leakage-related values		
Operating area (OP)	2.54 (0.22–31.02)	0.32 (0.06–0.76)
Patient's mouth (M)	32.81 (0.46–2150)*†	0.89 (0.32–11.42)
Anaesthesia machine (AM)	0.37 (0.26–3.36)	0.30 (0.05–0.92)

In the ET group, all *personnel-related* mean trace concentrations were less than isoflurane 2 ppm. In the LMA group at the locations of both the anaesthetist and the surgeon, one of 10 means exceeded this value. In the position occupied by the auxiliary nurse, three of 10 values exceeded 2 ppm. These higher values occurred during anaesthetic procedures in which values greater than isoflurane 100 ppm at the patient's mouth were measured. Any statistically significant differences in mean trace concentrations within the personnel-related measurement points and between the ET and LMA group were detected ($P < 0.05$).

Leakage-related values indicated that the artificial airway was the main leakage source in both groups. Trace concentrations were higher and variation was greater in the LMA group than in the ET group. The difference between the concentrations was statistically significant between the ET and LMA groups, and within the leakage-related LMA values at point M. Trace concentrations at locations AM and OP were comparable between the groups and within the leakage-related values.

Discussion

Some studies suggest that chronic exposure to trace concentrations of volatile anaesthetics may result in various forms of untoward health responses [8, 9]. The limitations of epidemiological studies have been discussed [10, 11]. Because of flaws in the epidemiological investigations and a lack of data concerning dose relationships, it has not been possible to establish an aetiological connection between such untoward health responses and waste anaesthetic gases [12].

To maintain low occupational exposure, NIOSH has also outlined a number of criteria for the workplace [1]. These criteria were fulfilled in this study. (1) The anaesthesia machine was connected to a central high-flow scavenging system (60 litre min^{-1}). (2) Leakage from the breathing system of a typical Draeger Sulla 808V was 22.8 ml min^{-1} [7],

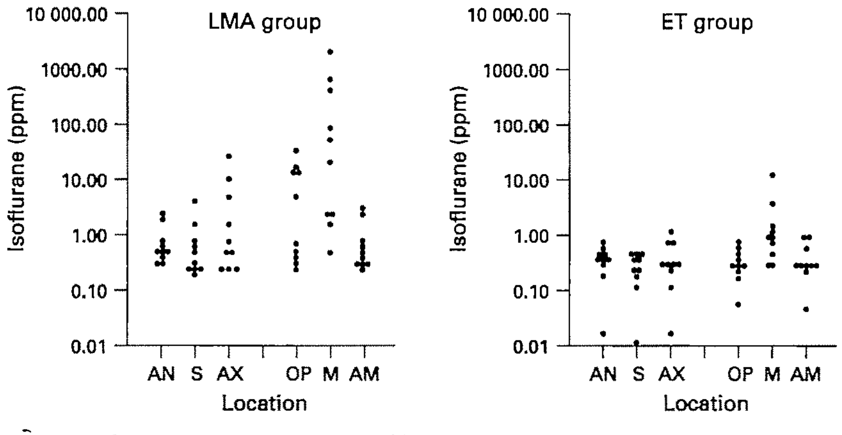

Figure 2 Distribution of mean trace concentrations of isoflurane at different locations (AN = anaesthetist, S = surgeon, AX = auxiliary nurse, OP = operating area, M = mouth of patient, AM = anaesthesia machine) in the LMA and ET groups.

far below the leakage value of 150 ml min^{-1} proposed by the Draft European Standard *Anaesthetic Workstations and Their Modules*. (3) Anaesthetic gas flow was started after insertion of the artificial airway (LMA or tracheal tube). Intermittent face mask ventilation with isoflurane was not performed. (4) Room ventilation comprised 20 changes per hour, with no air being recirculated. (5) The waste gas outlet of the anaesthetic gas monitor, a potential source of contamination [13], was connected to the hospital's central scavenging system (60 litre min^{-1}).

Trace concentrations of anaesthetics may be measured either off-line by gas chromatography or on-line using direct reading instruments. The system used in this study has some advantages over other direct reading instruments such as the MIRAN series. Using photoacoustic infrared spectrometry, detection levels are lower and accuracy is greater because of the possibility of cross-compensation for other gaseous substances present in the operating theatre. The Bruel and Kjaer 1302 photoacoustic infrared spectrometry system allows detection limits as low as isoflurane 0.009 ppm, with an accuracy of ±2% [14, 15].

Mean trace concentrations were calculated for each anaesthetic from the area under the curves derived from the intermittent measurements made by the measurement system, reflecting exposure during the period of anaesthetic administration neglecting, for example, intervals between operations. We believe this method may reflect accurately occupational exposure during anaesthesia; on the other hand, corrections to an 8-h working day can be performed easily or could be adapted to individual working shift conditions.

Leakage from the artificial airway appeared to be the main source of occupational exposure. In the LMA group, 60% of the mean values measured near the patient's mouths were greater than isoflurane 10 ppm. Peak concentrations exceeding 100 ppm were recorded in some cases, but there was no relation to higher ventilatory pressures in these cases. In the ET group, in one patient, isoflurane mean values exceeded 10 ppm. Variation of the mean values was less for the ET group than for the LMA group.

Trace concentrations recorded at the reservoir bag of the anaesthesia machine were all less than 5 ppm, which is consistent with the reportedly low leakage rate from the breathing system of this machine [7].

As expected with this type of surgery (eye surgery), because of the proximity of the measurement point "OP" to the main leakage source, point "M", mean values recorded at point "OP" probably do not reflect a specific contribution to air contamination.

Despite the high trace concentrations near the patient's mouth, most personnel-related mean trace concentrations were less than the strict NIOSH limit of 2 ppm of isoflurane. Higher mean trace concentrations (three of 10) at the position of the auxiliary nurse occurred during anaesthetic procedures in the LMA group in which substantial leakage from the patient's mouth was detected. In these patients, at the locations of both the anaesthetist and the surgeon, only one of 10 mean values exceeded 2 ppm. The higher levels for the auxiliary nurse could be explained by the position outside the main airflow of the air conditioning system and air movement from the laminar air flow field to the air exhausts in the corners of the operating theatre (fig. 1). The workplaces of the surgeon and anaesthetist, however, were within the main air flow, which probably explains why their mean concentrations were mainly less than 2 ppm in both groups.

With tracheal intubation, values of isoflurane in our study were less than those of other studies, which have reported concentrations of isoflurane 2.4–12 ppm [16], 3–11 ppm [17] and 13.4–21.0 ppm [18]. The higher values in these studies may be a result of less effective air conditioning systems, lack of a scavenging system or higher leakage from the anaesthesia machines [16–18].

Until now occupational exposure during general anaesthesia using the LMA has been measured only for nitrous oxide. Lambert-Jensen, Christensen and Brynnum found a higher, but non-significant difference in trace concentrations with controlled ventilation compared with spontaneous breathing. Nitrous oxide concentrations were 7.0–24.0 ppm under controlled ventilation and 7.5–18.4 ppm during spontaneous breathing [5]. Sarma and Leman reported that the LMA resulted in minimal theatre pollution during spontaneous ventilation. Nitrous oxide peak level ranged from 15 to 37 ppm [6].

A previous study on tracheal intubation and nitrous oxide pollution performed under identical working place conditions showed median trace concentrations at the personnel-related measurement points of 11.4–19.6 ppm [19].

We conclude that anaesthesia using the LMA in patients undergoing ventilation may be associated with high concentrations of isoflurane near the patient's mouth because of higher leakage rates. Using an effective high-flow scavenging system and air conditioning equipment that provided 20 changes of air per hour without recirculation, and a low-leakage anaesthesia machine, mean trace concentrations in the working environment may be almost as low as those associated with anaesthesia using tracheal intubation. Under other circumstances (e.g. lower air change rates), trace concentrations of isoflurane may be higher.

References

1. National Institute of Occupational Safety and Health. Criteria for a recommended standard: occupational exposure to waste anaesthetic gases and vapours. Cincinnati, Ohio: DHEW publication no. 77–140, 1977.
2. Brain A. The laryngeal mask: A new concept in airway management. *British Journal of Anaesthesia* 1983; **55**: 801–805.
3. Brain A, McGhee T, McAteer E, Thomas A, Abu-Saad M, Bushman J. The laryngeal mask airway: Development and preliminary trials of a new type of airway. *Anaesthesia* 1985; **40**: 356–361.
4. Devitt J, Wenstone R, Noel A, O'Donnell M. The laryngeal mask airway and positive pressure ventilation. *Anesthesiology* 1994; **80**: 550–555.

5. Lambert-Jensen P, Christensen N, Brynnum J. Laryngeal mask and anaesthetic waste gas exposure. *Anaesthesia* 1992; **47**: 697–700.
6. Sarma VJ, Leman J. Laryngeal mask and anaesthetic waste gas concentrations. *Anaesthesia* 1990; **45**: 791–792.
7. Leuenberger M, Feigenwinter P, Zbinden A. Gas leakage in eight anaesthesia circle systems. *European Journal of Anaesthesia* 1992; **9**: 121–127.
8. Cohen E, Brown B, Wu M. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *Journal of the American Dental Association* 1980; **101**: 21–31.
9. Guirguis S, Pelmear P, Roy M, Wong L. Health effects associated with exposure to anaesthetic gases in Ontario hospital personnel. *British Journal of Industrial Medicine* 1990; **47**: 490–497.
10. Ferstandig L. Trace concentrations of anesthetic gases: A critical review of their disease potential. *Anesthesia and Analgesia* 1978; **57**: 328–345.
11. Tannenbaum T, Goldberg R. Exposure to anaesthetic gases and reproductive outcome. *Journal of Occupational Medicine* 1985; **27**: 660–668.
12. Eger E. Fetal injury and abortion associated with occupational exposure to inhaled anesthetics. *AANA Journal* 1991; **59**: 309–312.
13. Lawson D, Jelenich S. Capnographs: a new operating room pollution hazard? *Anesthesia and Analgesia* 1985; **64**: 378.
14. Mollgaard K. Acoustic gas measurement. *Biomedical Instrumentation and Technology* 1989; **23**: 495–497.
15. Ghittori S, Fiorentino ML. Imbriani M. An evaluation of a new portable multi-gas monitor. *Applied Journal of Occupational Environmental Hygiene* 1993; **8**: 283–287.
16. Girompaire D, Landais A. Allegrini D. Pollution of operating rooms: Measurements made during five anaesthesias. *Cahiers d'Anesthesiologie* 1991; **39**: 253–256.
17. Imbriani M, Ghittori S, Pezzagno G, Capodaglio E. Evaluation of exposure to isoflurane (Forane): Environmental and biological measurements in operating room personnel. *Journal of Toxicology and Environmental Health* 1988; **25**: 393–402.
18. Flore C, Marchi A, Garau VL. Isoflurane pollution in operating rooms. *Giornale Italiano di Medicina del Lavoro* 1988; **10**: 107–110.
19. Hoerauf K, Koller C, Wiesner G, Taeger K, Hobbhahn J. Occupational exposure of operating theatre personnel to nitrous oxide. *Das Gesundheitswesen* 1995; **57**: 92–96.

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Ventilatory effects of eltanolone during induction of anaesthesia: comparison with propofol and thiopentone†

H. J. SPENS AND G. B. DRUMMOND

Summary

We recorded the ventilatory effects of eltanolone 0.75 mg kg^{-1}, propofol 2.5 mg kg^{-1} and thiopentone 4 mg kg^{-1} at induction of anaesthesia in 76 unpremedicated patients, aged 18–65 yr. Measurements were made using a pneumotachograph incorporated between a close-fitting face mask and a T-piece delivering 35% oxygen. Eltanolone caused significantly less apnoea than propofol (incidence 57% *vs* 100%) and less reduction in ventilation than propofol (median maximum decrease 4.8 *vs* 7.8 litre min^{-1}), but the differences between eltanolone and thiopentone were smaller and generally not significant. Ventilatory frequency was maintained well in the eltanolone group. (*Br. J. Anaesth.* 1996; **77**: 194–199).

Key words

Anaesthetics i.v., eltanolone. Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Ventilation, effects. Ventilation, apnoea.

The anaesthetic properties of some steroids have been recognized for more than 50 yr [1]. However, the development of these compounds for clinical use has been slow, because of adverse events with water-soluble agents [2–4] and the lack of a suitable solvent for lipid-soluble agents.

Eltanolone (3α-hydroxy-5β-pregnane-20-one, pregnanolone) has been known as a potent anaesthetic since 1957 [5]. An emulsion formulation of eltanolone, with the agent dissolved in the lipid phase of an oil–water emulsion, is now available (Careltan, Pharmacia). Potential advantages of this new drug, in comparison with currently available induction agents, include a high therapeutic ratio and lack of pain on injection. In addition, preliminary studies have reported less apnoea [6, 7], in keeping with findings with earlier steroid induction agents [8, 9].

Lack of depression of ventilation is advantageous in anaesthesia if neuromuscular blocking agents are not used, allowing smooth transition from i.v. to inhalation anaesthesia and helping to prevent hypoxia. The aim of this study was to investigate the ventilatory effects of eltanolone at induction of anaesthesia, and to compare these effects with those of propofol and thiopentone.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 76 ASA I and II patients, of both sexes, aged 18–65 yr, undergoing elective surgery. We excluded patients who were more than 50% above ideal weight for height (Metropolitan Life Insurance Company tables), pregnant, who had significant respiratory disease, anaesthetic drug allergy, who abused alcohol or other substances or who were receiving any medicines which might affect ventilation. Patients received no premedication and were allocated randomly to receive eltanolone 0.75 mg kg^{-1}, propofol 2.5 mg kg^{-1} or thiopentone 4 mg kg^{-1} for induction of anaesthesia. These doses have been shown to be approximately equipotent [7, 10].

After arrival in the anaesthetic room an i.v. cannula was inserted. Inductance bands were positioned around the chest and abdomen and connected to a respiratory inductance plethysmograph. The signals, representing dimensional changes in the rib cage and abdomen with respiration, were recorded using commercial respiratory monitoring software (Cardas, version 2.07 advanced, Oxcams, Oxford), running in MS-DOS (version 6.20), onto a lap-top computer. These bands allowed detection of upper airways obstruction by comparison of chest wall movement and respired volumes. Patients lay on a mattress filled with polystyrene beads that was made rigid to prevent body movement (Vac-Pac, Howmedica). Patients breathed 35% oxygen from a T-piece, through a screen pneumotachograph (F100L, Mercury Electronics) and a tight-fitting face mask with a wide pneumatic seal (Downs CPAP mask No. 9002, Vital Signs Inc., NJ, USA), held in place with both hands by the anaesthetist. The pneumotachograph was connected to a differential pressure transducer (±10 mm H_2O), Furness) and the resulting flow signal was also recorded. The system was calibrated in the laboratory using a series RT200 calibration analyser (Timeter Instrument Corporation, Missouri, USA) and was linear up to 40 litre min^{-1}. Immediately before each study, the

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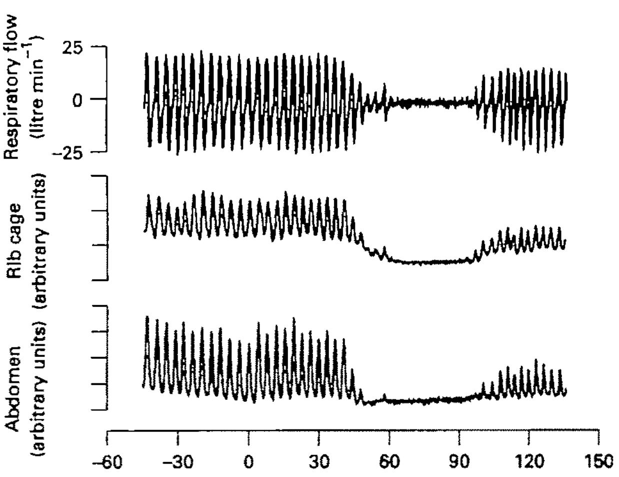

Figure 1 Part of a typical recording, with respiratory flow and dimensions of the rib cage and abdomen. The induction agent was given over 30 s, starting at time 0.

calibration was checked against a flowmeter (its accuracy had also been verified in the laboratory) and was considered acceptable if the error was less than ±5%. A pulse oximeter (Ohmeda Biox 3700) was used to measure oxygen saturation and heart rate and these signals were also recorded on the computer.

After a period of 3–5 min of stable breathing, the induction agent was administered over 30 s. Lignocaine 10 mg was mixed with propofol to prevent pain on injection. The moment of loss of consciousness was noted from when the patient dropped a metal rod held between the thumb and index finger. If consciousness was not lost within 120 s further anaesthetic was given and the patient was withdrawn from the study. The patient's jaw was supported gently by the anaesthetist to prevent upper airway obstruction. Recordings were continued for 4 min from the start of induction or until the patient showed signs of arousal when a further dose of induction agent was administered. Any adverse events which occurred, including apnoea, were noted. After completion of this study, anaesthesia was continued as appropriate for clinical management. A tracing of part of a typical study is shown in figure 1.

The flow signal was then analysed by a locally written computer program which calculated breath by breath values for tidal volume (V_T), respiratory frequency (f), inspiratory time (T_I) and expiratory time (T_E). Mean values over 30 s were calculated every 30 s from the start of administration of the induction agent. Minute ventilation (V_E) was then obtained from the product of V_T and f. A stable 30-s period, approximately 2 min before the start of induction, was used to calculate control values.

Adverse events during anaesthesia were noted. All patients were visited approximately 24 h after operation and returned a questionnaire 2 weeks later to determine if any side effects had occurred. They were asked specifically about the severity and duration of nausea and vomiting, dizziness or lightheadedness, headaches, sore throat, rashes or drip site inflammation, muscle pains and cough.

Data were analysed using the Minitab statistical package (release 8.2), running in MS-DOS (version 6.20). Non-parametric tests of significance were used to compare the three groups and changes from baseline (Kruskal–Wallis, Mann–Whitney, Wilcoxon signed rank sum and chi-square as appropriate). With 23 patients per group the estimated power of the study to detect a difference in ventilation of 2 litre min^{-1} at a significance level of 0.05 was 0.8.

Results

Of the 76 patients recruited, results were available for analysis from 69, 23 per group. Two patients in the propofol group were excluded because of study violations, two patients (one eltanolone, one propofol) developed upper airway obstruction after induction of anaesthesia, shown by normal or increased chest wall movements with absent or reduced flow, and therefore were excluded, data from two patients in the thiopentone group could not be analysed because their breathing patterns were too irregular, and one patient's operation was cancelled after randomization to receive eltanolone.

The characteristics of those included are shown in table 1. The propofol group contained more males and the thiopentone group more females than the eltanolone group, with a corresponding bias in height and weight.

Induction of anaesthesia was successful in all patients, and the time from the start of administration of the induction agent to loss of consciousness was similar in the three groups (means 45.8, 43.5 and 45.3 s in the eltanolone, propofol and thiopentone groups, respectively).

The incidence of apnoea and the median duration of absent breathing are shown in table 2. Differences

Table 1 Patient characteristics (mean (SD or range) or number)

	Eltanolone (n = 23)	Propofol (n = 23)	Thiopentone (n = 23)
Age (yr)	37.1	37.5	37.3
	(18–58)	(22–54)	(20–64)
Height (cm)	172	175	169
	(9.4)	(8.4)	(9.4)
Weight (kg)	70.8	73.2	65.5
	(9.2)	(10.5)	(12.6)
Sex (M:F)	13:10	16:7	7:16

Table 2 Incidence of apnoea and duration of absent breathing in the three groups (number (%) or median (quartiles))

	Eltanolone (n = 23)	Propofol (n = 23)	Thiopentone (n = 23)
Number (%) apnoeic episodes			
Any duration	13	23	17
	(57)	(100)	(74)
> 30 s	7	17	9
	(30)	(74)	(39)
> 60 s	3	15	5
	(13)	(65)	(22)
Duration of absent breathing (s)	6 (0,41)	88 (30,113)	22 (0,43)

Table 3 Respiratory variables for the three groups for each time period (median (quartiles)). Statistical differences ($P < 0.05$) between drug groups are indicated (* eltanolone *vs* propofol, † eltanolone *vs* thiopentone, ‡ propofol *vs* thiopentone). All values of minute volume and tidal volume were significantly reduced from baseline from 60 s onwards. Frequency was reduced significantly from baseline at 60–120 s in the propofol group, and at 60–90 s in the thiopentone group. From 150 s in the eltanolone group, 180 s in the propofol group and at 240 s in the thiopentone group, ventilatory frequency was significantly greater than baseline

Variable	Drug	Baseline	30 s	60 s	90 s	120 s	150 s	180 s	210 s	240 s	Maximum reduction
Minute volume (litre min^{-1})	Eltanolone	7.9 (6.9, 8.4)*	7.7 (6.7, 9.5)*	4.0 (0.5, 9.0)*†	3.3 (1.3, 5.0)*	4.2 (3.5, 5.3)*	4.6 (3.9, 6.1)*	5.0 (4.5, 6.8)	5.6 (4.7, 6.9)	5.65 (4.9, 7.3)	4.8 (2.9, 7.3)*
	Propofol	8.2 (7.7, 11.4)‡	9.9 (7.6, 12)‡	0.7 (0, 2.1)	0 (0, 1.0)‡	0 (0, 4.9)‡	3.6 (0, 5.3)‡	4.5 (2.1, 6.1)	5.6 (3.9, 6.6)	5.4 (4.0, 6.7)	7.8 (7.1, 11.4)‡
	Thiopentone	7.2 (6.3, 8.0)	7.3 (5.9, 9.2)	1.4 (0, 2.4)	2.9 (0.2, 5.2)	4.7 (0.4, 6.2)	5.3 (3.8, 6.0)	5.45 (3.6, 6.5)	4.9 (4.0, 6.3)	5.3 (4.6, 6.2)	6.1 (4.0, 8.0)
Tidal volume (ml)	Eltanolone	570 (458, 656)	550 (474, 627)	352 (99, 442)	201 (151, 288)*	215 (173, 291)*	245 (216, 289)†	282 (236, 299)	297 (245, 321)	291 (252, 348)	399 (247, 585)*
	Propofol	661 (540, 921)‡	716 (519, 834)‡	224 (0, 382)	0 (0, 174)‡	0 (0, 248)‡	182 (0, 310)‡	219 (145, 334)‡	251 (195, 350)	263 (208, 343)	661 (383, 921)‡
	Thiopentone	471 (407, 643)	500 (319, 649)	147 (0, 407)	211 (12, 328)	254 (89, 381)	313 (244, 368)	319 (245, 424)	291 (244, 384)	302 (235, 381)	378 (244, 528)
Frequency (b.p.m.)	Eltanolone	14 (12, 15)	15 (12, 16)	13 (2, 19)*	16 (8, 21)*	20 (14, 23)*†	21 (14, 23)*	21 (16, 24)†	21 (16, 23)†	21 (17, 24)†	4 (0, 12)*
	Propofol	14 (12, 17)	15 (13, 19)	2 (0, 6)	0 (0, 10)‡	0 (0, 19)	11 (0, 20)	19 (15, 23)	19 (16, 22)	19 (16, 22)	12 (10, 15)
	Thiopentone	15 (12, 17)	16 (12, 19)	4 (0, 13)	10 (6, 17)	16 (4, 20)	16 (14, 20)	16 (14, 20)	17 (14, 20)	17 (15, 21)	9 (3, 14)

between the eltanolone and propofol groups were highly significant ($P < 0.01$) but differences between the eltanolone and thiopentone groups were not.

Table 3 shows the respiratory variables measured. Baseline ventilation and tidal volume were greater in patients who received propofol, probably because of the preponderance of males in this group. In all groups there was a significant reduction from baseline in both minute volume and tidal volume from 60 s onwards. The maximum reduction in minute ventilation in the eltanolone group was significantly less than that in the propofol group (median 4.8 *vs* 7.8 litre min^{-1}), but was not significantly different from the thiopentone group (6.1 litre min^{-1}). Similarly, tidal volumes were depressed to a greater extent in the propofol group.

Ventilatory frequency, however, exhibited a somewhat different pattern. In the eltanolone group it did not decrease below baseline values, unlike the propofol and thiopentone groups where it was significantly below baseline at 60–120 s and 60–90 s, respectively. The difference between eltanolone and propofol was significant at 60–150 s. In all groups ventilatory frequency increased above baseline towards the end of the study and this effect was most marked in the eltanolone group and least in the thiopentone group.

We also analysed the minimum value of minute ventilation in each patient after injection. The median minimum minute ventilation was 3.3 litre min^{-1} (interquartile range 0–4.5 litre min^{-1}) in the eltanolone group, 0 (0–0.6) litre min^{-1} in the propofol group and 0.7 (0–2.4) litre min^{-1} in the thiopentone group. The minimum minute ventilation tended to be reached later in the eltanolone group (median 90 s from the start of injection) than in the two other groups (median 60 s). The difference in treatment effect between eltanolone and propofol was highly significant ($P < 0.01$), but the difference between eltanolone and thiopentone was not ($P = 0.09$).

Summary spirograms have been drawn to allow comparison of the pattern of breathing after each drug, using baseline measurements and values at 180 s (fig. 2). This time period was chosen for analysis because it was the first after injection where spontaneous respiration had restarted in most patients. Inspiratory time (*T*I) was reduced more in the eltanolone and propofol groups at 180 s compared with the thiopentone group ($P < 0.05$), corresponding to the increase in ventilatory frequency observed in these patients. Inspiratory drive, expressed by the gradient of the inspiratory line (*V*T/*T*I), was reduced more in the propofol group than in the eltanolone or thiopentone groups, but this difference was not significant.

There were no serious adverse events during the study, but several minor side effects were noted. Table 4 summarizes the adverse events during anaesthesia. Involuntary movement occurred in 10 patients who had received eltanolone and in four who had received propofol. These were graded as moderate in three of the eltanolone group and mild in the remainder. They lasted between a few seconds and several minutes, terminated spontaneously in all

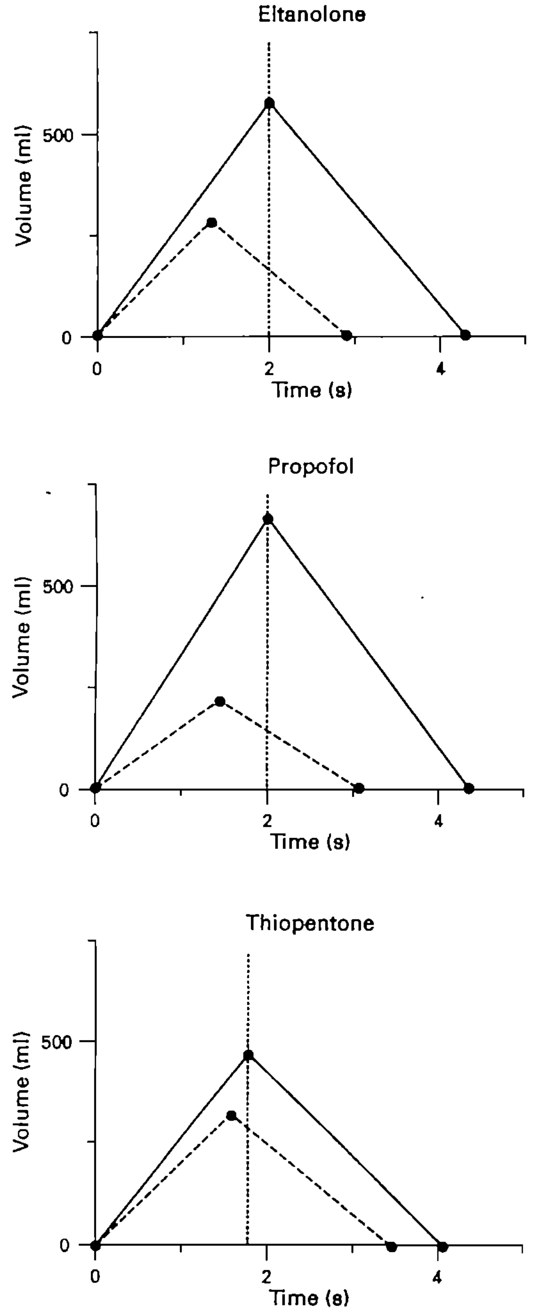

Figure 2 Summary spirograms for each drug; —— = baseline, - - - = 180 s. V_T/T_I was relatively well preserved with eltanolone and thiopentone compared with propofol, while T_I was better preserved in the thiopentone group.

cases and did not cause any clinical difficulty. Additionally, two patients in the eltanolone group developed hypertonus of the neck or upper limbs.

Flushing occurred in two patients in the eltanolone group and in one patient in each of the other treatment groups. However, in all cases this occurred after the end of the study and was related temporally to the administration of other drugs known to release histamine rather than administration of the induction agent.

Six patients who had received eltanolone coughed during the anaesthetic, compared with two who had received propofol and three who had received thiopentone. Additionally, one patient in the eltanolone group developed laryngospasm and one patient in the propofol group developed bronchospasm. However, these adverse events were not generally attributable to the induction agent, but usually occurred if the inspired concentration of isoflurane was increased rapidly. Oxygen saturation decreased to less than 85% as a result of coughing in one patient after propofol, and because of prolonged apnoea in five patients who received propofol and one patient who received thiopentone.

Table 4 Incidence (%) of adverse events during anaesthesia (all patients)

	Eltanolone ($n = 24$)	Propofol ($n = 26$)	Thiopentone ($n = 25$)
Involuntary movements	10 (42)	4 (15)	0
Muscle rigidity	2 (8)	0	0
Flushing	2 (8)	1 (4)	1 (4)
Tachycardia	10 (42)	2 (8)	0
Cough	6 (25)	2 (8)	3 (12)
Laryngospasm	1 (4)	0	0
Bronchospasm	0	1 (4)	0
$Sp_{O_2} < 85\%$	0	6 (23)	1 (4)

Table 5 Incidence (%) of adverse events after anaesthesia (all patients)

	Eltanolone ($n = 24$)	Propofol ($n = 26$)	Thiopentone ($n = 25$)
Nausea	7 (29)	4 (15)	9 (36)
Vomiting	4 (17)	1 (4)	6 (24)
Dizzy or lightheaded	6 (25)	5 (19)	6 (24)
Headache	3 (13)	4 (15)	0
Sore throat	2 (8)	4 (15)	0
Red/bruised i.v. site	2 (8)	1 (4)	0
Cough	1 (4)	0	0
Muscle pain	0	1 (4)	0
Other	6 (25)	6 (23)	7 (28)

Tachycardia (> 100 beat min^{-1}) was more common after eltanolone, occurring in 10 patients compared with only two after propofol and none after thiopentone. However, this was probably directly attributable to eltanolone in only two cases, with insufficient depth of anaesthesia and other anaesthetic agents being more likely causes in all other cases.

Adverse events reported after operation are shown in table 5. Nausea and vomiting were the most frequently described side effects, with a greater incidence reported in the eltanolone and thiopentone groups than in the propofol group, but the differences were not significant. Similar numbers of patients in each group complained of dizziness, while the incidence of all other side effects was low and distributed fairly evenly between the three groups.

Discussion

Our results confirmed that induction of anaesthesia with eltanolone in unpremedicated patients produced much less depression of ventilation than an equipotent dose of propofol, in terms of reduction of minute volume, incidence of apnoea and duration of absent breathing. Ventilatory depression with eltanolone was also less than that with thiopentone, but this was significant only at 60 s, with no significant difference in either the maximum reduction or minimum minute ventilation recorded. Ventilatory frequency was better maintained with eltanolone than with either of the two drugs, and was increased significantly from baseline from 150 s onwards.

A larger sample size might have revealed a difference between eltanolone and thiopentone. When we designed the study we calculated that a sample size of 69 would give a power of 0.8 to detect a difference of 2 litre in minute ventilation, at a significance level of 0.05, given an SD for ventilation of 2.2 litre min^{-1}. However, there was considerable variation in the reduction of ventilation, and the power of the study to detect a real difference in ventilation of 2 litre min^{-1} was only approximately 0.75.

We found that the baseline value of minute volume was significantly greater in the propofol than in the eltanolone and thiopentone groups (median 8.2 *vs* 7.9 and 7.2 litre min^{-1}, respectively). This was probably because of the difference in sex distribution between the three groups, and we do not consider the difference to be clinically important.

In any study of ventilation using a face mask there is potential for measurement error for several reasons. Unrecognized mask leaks are one possible source of inaccuracy. To minimize this we used a face mask with a wide pneumatic rim, applied water soluble jelly to improve the seal if facial stubble was present, and held the mask firmly in place using two hands, allowing manual detection of escaping gas. Use of an end-tidal carbon dioxide monitor in a few patients showed normal waveforms and end-tidal values, confirming our belief that significant gas leaks did not occur. The measurement apparatus may itself induce changes in ventilatory pattern [11], but this effect is least when a face mask with high fresh gas flow is used, as in our system, and is less relevant when comparing groups as all patients would be equally affected. We did not make any recordings of arterial pressure during the study as we believe that inflation of a pneumatic cuff on the arm may have been sufficiently stimulating to affect respiratory pattern.

Further investigation of eltanolone may provide different estimates of the relative potency, which could alter the interpretation of our results. Also, although administration of a pre-calculated bolus dose of induction agent over approximately 30 s is common clinical practice, other methods, for example less rapid administration to a clinical end-point such as cessation of counting, could result in different dose requirements and ventilatory effects [12–14].

Direct comparison of our results with other studies is difficult because of both the variable doses administered and the different premedications used in earlier work. Additionally, our study is the first which has been designed to examine specifically the ventilatory effects of eltanolone, and therefore the only previous eltanolone data available for comparison are observations of apnoea.

Using eltanolone 0.75 mg kg^{-1} we found that 30 % of patients were apnoeic for greater than 30 s, with 13 % being apnoeic for more than 60 s. This is a greater incidence than reported by many earlier authors [6, 7, 15, 16] but, except for one study [16], smaller doses of eltanolone were used. After a prior dose of fentanyl, and a dose of 0.59–0.89 mg kg^{-1}, given over a range of times, Myint, Peacock and Reilly [12] reported that 37 % of their patients were apnoeic for more than 30 s. All patients studied by Kallela and colleagues [17] using eltanolone 0.8 mg kg^{-1} were apnoeic for more than 60 s, probably because of the generous dose of alfentanil given before induction.

There are some data available on the ventilatory effects of earlier steroid induction agents, and in general the pattern we have seen with eltanolone is similar. Hall, Whitwam and Morgan [18], using Althesin 50 and 100 µl kg^{-1} after either diazepam or papaveretum premedication, found an incidence of apnoea of 41 %, lasting 8–102 s, compared with an incidence of 56.5 %, lasting 4–119 s, in our study. Additionally, they described a significant reduction in minute ventilation at 2 and 3 min after induction of anaesthesia with Althesin, with an increase in ventilatory frequency above baseline after 3 min in the non-opioid groups, which are similar to our own observations with eltanolone. However, Campbell and colleagues [19], using Althesin 100–150 µl kg^{-1} in unpremedicated patients, did not observe apnoea, but described a similar increase in ventilatory frequency. Savege and colleagues [8], using Althesin 50 µl kg^{-1}, also found an increase in ventilatory frequency after a period of apnoea averaging 23 s. With minaxolone 0.4 mg kg^{-1} [9], a similar picture was seen, with a 25 % incidence of apnoea of short duration, an increase in ventilatory frequency in the non-opioid group, and a decrease in minute ventilation.

Our study confirms earlier work suggesting that both propofol and thiopentone are ventilatory depressants [8, 20–23]. However, in general, we demonstrated a greater effect than these earlier studies, in spite of the similar or lower doses we used and the fact that our patients were unpremedicated. The reasons for this are unclear, but the higher frequency of observations which we used, the different measurement techniques and the lower baseline ventilation in some of these studies may all have contributed. Previous reports comparing propofol with thiopentone conflict as to whether or not a difference exists between their ventilatory effects; our results suggest that propofol is a more potent respiratory depressant than thiopentone.

The increase in ventilatory frequency found towards the end of our study when anaesthetic depth was presumably less, is consistent with previous work using a variety of agents [8, 9, 18, 20, 24–26]. The mechanism of this effect is uncertain, but it has been postulated that increased excitability of the inspiratory "off-switch" is responsible [24]. Some steroid hormones are known to be respiratory stimulants [27] which may contribute to the enhanced effect we found with eltanolone; however the similarity of this augmentation to that seen with propofol, when respiration restarts, raises the possibility that the lipid emulsion itself may contribute.

We conclude that the modest ventilatory depression seen after induction of anaesthesia with eltanolone may be useful in allowing a smooth transition to inhalation anaesthesia and may also indicate a role in sedation. The only frequent side effect was involuntary movement, but this was never troublesome and should not affect the value of this new agent.

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References

1. Selye H. Anesthetic effect of steroid hormones. *Proceedings of the Society of Experimental Biology and Medicine* 1941; **46**: 116–121.
2. Robertson JD, Wynn Williams A. Studies on the clinical and pathological effects of hydroxydione. *Anaesthesia* 1961; **16**: 389–409.
3. Atkinson RM, Davis B, Pratt MA, Sharpe HM, Tomich EG. Action of some steroids on the central nervous system of the mouse. 11. Pharmacology. *Journal of Medicinal Chemistry* 1965; **8**: 426–432.
4. Sear JW, Prys-Roberts C, Gray AJG, Walsh EM, Curnow JSH, Dye J. Infusions of minaxolone to supplement nitrous oxide–oxygen anaesthesia. A comparison with Althesin. *British Journal of Anaesthesia* 1981; **53**: 339–350.
5. Figdor SK, Kodet MJ, Bloom BM, Agnello EJ, P'An SY, Laubach GD. Central activity and structure in a series of water soluble steroids. *Journal of Pharmacology and Experimental Therapeutics* 1957; **119**: 299–309.
6. Rajah A, Powell H, Morgan M. Eltanolone for induction of anaesthesia and to supplement nitrous oxide for minor gynaecological surgery. *Anaesthesia* 1993; **48**: 951–954.
7. Van Hemelrijck J, Muller P, Van Aken H, White PF. Relative potency of eltanolone, propofol, and thiopental for induction of anesthesia. *Anesthesiology* 1994; **80**: 36–41.
8. Savege TM, Ross L, Foley EI, Maxwell MP. A comparison of the cardiorespiratory effects during induction of anaesthesia of Althesin with thiopentone and methohexitone. *Postgraduate Medical Journal* 1972; **48** (Suppl. 2): 66–72.
9. Puchihewa VG, Whitwam JG, Morgan M, Lumley J. Respiratory effects of minaxolone. *Anaesthesia* 1980; **35**: 611–613.
10. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
11. Maxwell DL, Cover D, Hughes JMB. Effect of respiratory apparatus on timing and depth of breathing in man. *Respiration Physiology* 1985; **61**: 255–264.
12. Myint Y, Peacock JE, Reilly CS. Induction of anaesthesia with eltanolone at different rates of infusion in elderly patients. *British Journal of Anaesthesia* 1994; **73**: 771–774.
13. Drummond GB. Reduction of tonic ribcage muscle activity by anesthesia with thiopental. *Anesthesiology* 1987; **67**: 695–700.
14. Rolly G, Versichelen L, Huyghe L, Mungroop H. Effect of speed of injection on induction of anaesthesia using propofol. *British Journal of Anaesthesia* 1985; **57**: 743–746.
15. Powell H, Morgan M, Sear J. Pregnanolone: a new steroid intravenous anaesthetic. *Anaesthesia* 1992; **47**: 287–290.
16. Gray HSJ, Holt BL, Whitaker DK, Eadsforth P. Preliminary study of a pregnanolone emulsion (KABI 2213) for i.v. induction of general anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 272–276.
17. Kallela H, Haasio J, Korltila K. Comparison of eltanolone and propofol in anesthesia for termination of pregnancy. *Anesthesia and Analgesia* 1994; **79**: 512–516.
18. Hall GM, Whitwam JG, Morgan M. Some respiratory effects of Althesin. *British Journal of Anaesthesia* 1973; **45**: 629–632.
19. Campbell D, Forrester AC, Miller DC, Hutton I, Kennedy JA, Lawrie TDV, Lorimer AR, McCall D. A preliminary clinical study of CT1341—a steroid anaesthetic agent. *British Journal of Anaesthesia* 1971; **43**: 14–24.
20. Germain M, Wahba WM, Gillies DMM. Ventilation following induction of general anaesthesia by thiopentone. *Canadian Anaesthetists Society Journal* 1982; **29**: 100–104.
21. Whitwam JG. A clinical comparison of the incidence and duration of apnoea following methohexitone and thiopentone. *British Journal of Anaesthesia* 1962; **34**: 729–732.
22. Taylor MB, Grounds RM, Mulrooney PD, Morgan M. Ventilatory effects of propofol during induction of anaesthesia. Comparison with thiopentone. *Anaesthesia* 1986; **41**: 816–820.
23. Grounds RM, Maxwell DL, Taylor MB, Aber V, Royston D. Acute ventilatory changes during i.v. induction of anaesthesia with thiopentone or propofol in man. Studies using inductance plethysmography. *British Journal of Anaesthesia* 1987; **59**: 1098–1102.
24. Gautier H, Gaudy JH. Changes in ventilatory pattern induced by intravenous anaesthetic agents in human subjects. *Journal of Applied Physiology* 1978; **45**: 171–176.
25. Goodman NW, Black AMS, Carter JA. Some ventilatory aspects of propofol as sole anaesthetic agent. *British Journal of Anaesthesia* 1987; **59**: 1497–1503.
26. Choi SD, Spaulding BC, Gross JB, Apfelbaum JL. Comparison of the ventilatory effects of etomidate and methohexital. *Anesthesiology* 1985; **62**: 442–447.
27. Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. *Journal of Applied Physiology* 1993; **73**: 393–404.

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Effect of anaesthesia on lung function in children with asthma

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Summary

Spirometry was performed before operation, soon after recovery ("early") and the day after ("late") general anaesthesia for elective surgery in 20 children with asthma and 20 matched children without asthma. Pulse oximetry was recorded on the first postoperative night. The mean early peak expiratory flow rate (PEFR) decreased in the asthmatics by 19.91 (95% confidence intervals (CI) 10.84–28.97)% and in the controls by 19.25 (10.70–27.80)%. The mean early FEV_1 decreased in the asthmatics by 16.02 (9.29–22.75)% and in the controls by 11.03 (2.86–19.19)%. The mean late decrease from baseline PEFR for the asthmatics was 18.55 (11.23–25.87)% but only 14.93 (7.89–21.97)% for the controls. The mean late FEV_1 was 8.2 (0.83–15.56)% below baseline in the asthmatics but only 6.82 (−0.79 to 14.42)% in the controls. There were no differences in overnight pulse oximetry. We conclude that healthy children exhibited a decrease in FEV_1 and PEFR after general anaesthesia for elective surgery, but this decline did not appear to be any greater in well controlled asthmatic children compared with children who did not have asthma. (*Br. J. Anaesth.* 1996; **77**: 200–202)

Key words

Asthma. Children. Anaesthesia, paediatric. Monitoring, spirometry. Lung, function.

There is a high prevalence of asthma in childhood; a recent study from Scotland showed a prevalence of greater than 14% [1]. With an increase in the range of surgical, investigative and therapeutic procedures requiring general anaesthesia, this suggests that many children with asthma are being exposed to general anaesthesia for both elective and emergency procedures. Inhalation agents have been shown to attenuate provoked increases in airways resistance and decreases in lung compliance in dogs [2] and in humans [3, 4], and have been used to treat acute bronchospasm [5, 6]. Animal studies have shown that neuromuscular blockers have variable effects on pulmonary resistance [7]. Opioids cause central respiratory depression, and some opioid drugs cause histamine-mediated bronchospasm. To our knowledge these effects have not been studied in children with asthma.

The aim of this study was to measure the effect of balanced general anaesthesia on respiratory function of children with asthma, compared with a group of children who did not have asthma. We also compared the patterns of postoperative overnight pulse oximetry in these two groups.

Patients and methods

The study was approved by the Research Ethics Committee of the Royal Liverpool Children's Hospital NHS Trust.

We studied all patients (the asthma group and controls) presenting for elective surgical procedures requiring general anaesthesia, aged 5–16 yr, and able to perform spirometry. All were free from intercurrent infection or respiratory illness at the time of study. In the asthma group, all children were previously diagnosed as having asthma, and were receiving prophylactic treatment with either inhaled sodium cromoglycate or inhaled corticosteroids.

The control group comprised 20 children, with no previous diagnosis of asthma. Children were excluded from the control group if they had a history of recurrent cough, wheeze or atopy.

Each asthmatic child was matched with a control for date of birth (within 1 yr), sex and type of operation (nose, throat or dental surgery, for example tonsillectomy, extraction of teeth; body surface or limb surgery, for example arthroscopy of the knee, removal of metalwork from limb; minor lower abdominal surgery, for example orchidopexy, herniotomy). Children undergoing major abdominal or cardiothoracic surgery were not studied. The technique of anaesthesia varied according to the operative procedure, however, each control child received an anaesthetic similar to that of the matched asthmatic child, including premedication, method of induction, volatile agent, airway management, neuromuscular block, method of ventilation and intraoperative analgesia. Postoperative analgesia was prescribed according to the type of surgery and size of the child, and administered on individual request. Regular medication was continued in the perioperative

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period, but additional specific bronchodilator therapy was not prescribed, unless the clinical need arose.

The children were visited before operation, with a parent present, by one of the investigators, and written informed consent was obtained from the child (if appropriate), and parent.

Spirometry was performed during the preoperative visit using the portable Vitalograph Compact II (Vitalograph Ltd, Buckingham, UK). Values for peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and the ratio FEV_1/FVC, were obtained for each child after training in the correct technique. These were expressed as percentage of predicted values for height, age and sex [8]. This was repeated in the "early" postoperative period (sufficient recovery from anaesthesia to facilitate full effort at spirometry) and again in the "late" postoperative period (the following morning after 08:30 but before discharge). Spirometry measurements were carried out by one of three investigators (H.A.M., P.H.M. or H.C.R.), all of whom were trained in the lung function laboratory at the hospital.

On the first night after operation, pulse oximetry was recorded continuously for 8 h using the Ohmeda 3700e device (Ohmeda Ltd, Louisville, USA). The trend data from this monitor were downloaded onto a disk for analysis to produce a report of range, mean and frequency distribution of oxygen saturation. Of the 20 pairs studied, overnight pulse oximetry was completed only in 11 pairs.

Data were analysed by Wilcoxon signed ranks matched pairs test. Postoperative spirometry values were subtracted from baseline values and the size of the difference was analysed within each group. Paired comparisons of changes in lung function between asthmatics and controls were performed by subtracting the percentage decrease in FEV_1 or PEFR in the early or late postoperative period for each control from the percentage decrease in FEV_1 or PEFR at the same time for the asthmatic with whom they were matched. These differences were compared using the paired Student's *t* test.

Results

The asthmatic and control groups were comparable in age, weight, height and duration of operation. Preoperative PEFR and FEV_1 were also similar (table 1).

Table 1 Patient characteristics and preoperative PEFR and FEV, values in asthmatics and controls (mean (range))

	Asthmatics	Controls
Age (yr)	10.1 (6.5–15.1)	10.1 (5.5–16.0)
Height (cm)	136 (111–165)	140 (104–173)
Weight (kg)	34.9 (19.5–58.9)	36.8 (16.0–61.0)
Duration of operation (min)	38 (10–135)	46.6 (20–90)
Preop. PEFR (% predicted)	89.7 (60–115)	81.1 (70–117)
Preop. FEV_1 (% predicted)	88.3 (45–138)	85.0 (65–111)

In both groups there was a decrease in PEFR and FEV_1 in the early postoperative period, and in PEFR in the late postoperative period, which was greater than 10% and statistically significant. The decrease in FEV_1 in the late postoperative period was less than 10% in both groups, although this decrease did reach statistical significance in the asthmatics (table 2).

There was no significant difference between the groups in the decline in PEFR or FEV_1 at either postoperative time (data not shown).

Overnight pulse oximetry readings were similar for the asthmatics and controls in the 11 pairs studied. The mean difference in percentage oxygen saturation between asthmatics and controls was −0.03 (95% confidence interval −0.8 to 0.7) and the mean difference in time spent with oxygen saturations less than 90% was 0.87 (95% CI −0.1 to 1.9) h. These differences were not significant.

Discussion

To our knowledge this is the first study to investigate the overall effect of balanced general anaesthesia on lung function in children with asthma. We have demonstrated that healthy children, both asthmatics and non-asthmatics, undergoing general anaesthesia for elective surgery showed a decline in FEV_1 and PEFR in the early postoperative period. There was no difference in overnight oxygen saturation between the groups, and no clinical problems were observed in any patient.

Children with asthma are usually familiar with performing peak expiratory flow tests, and many have been taught how to perform spirometry tests. However, children who have never been suspected of having a respiratory disease will not have performed spirometry other than in this study. The control group had lower values for preoperative PEFR and FEV_1, and although these were not statistically significant, this may reflect a less practised technique. However, as measurements were recorded only after careful training had been completed, and consistent results were achieved for each child, this effect was minimized. We found no difference between the groups in preoperative baseline spirometry, which would indicate that the asthmatic children were well controlled with their current medication.

Both groups demonstrated the greatest decrease in PEFR and FEV_1 in the early postoperative period, when impaired co-operation secondary to results anaesthesia may have contributed to lower values. However, measurements were made only when it was considered that adequate consciousness had returned, and co-operation was similar to preoperative levels. The mean decreases in early postoperative PEFR and FEV_1 were greater than 10% in the asthmatics and controls and, as such, may be considered clinically and statistically significant. The decrease in FEV_1 in the late postoperative period was less than 10% in both groups. Although this late decrease in FEV_1 was statistically significant in the asthmatics, there was no statistically significant difference between asthmatics and controls, and it is

Table 2 Percentage decreases in PEFR and FEV_1 from baseline (mean (95% confidence intervals)). *P* values relate to significance of decreases from baseline

	Asthmatics	*P*	Controls	*P*
"Early" PEFR	19.9 (10.8–29.0)	0.001	19.3 (10.7–27.8)	0.04
"Early" FEV_1	16.0 (9.3–22.8)	0.0007	11.0 (2.9–19.2)	0.001
"Late" PEFR	18.6 (11.2–25.9)	0.0007	14.9 (7.9–22.0)	0.03
"Late" FEV_1	8.2 (0.8–15.6)	0.007	6.8 (−0.8 to 14.4)	0.12

unlikely to be clinically significant. The reduction in PEFR in the early postoperative period was accompanied by decreases of greater than 10% in FEV_1 (which is much less effort dependent than PEFR) [9] in the same period.

The small decreases in PEFR and FEV_1 were not associated with clinical problems and may represent small airways collapse caused by mucous plugging or bronchoconstriction. It is possible that in less well controlled asthmatics, with a preoperative deterioration in FEV_1, a similar decline in FEV_1 would cause clinical problems.

Statistical comparison of the differences between the groups for all decreases in PEFR and FEV_1 showed no significant differences at any time. With 20 pairs this study had a power of 0.7 to detect a difference of 10% in early FEV_1 between the asthmatics and controls. A study with a power of 0.9 to find a difference of 10% would require 33 pairs. In this large specialist paediatric centre, recruitment of 20 matched pairs took more than 2.5 yr and became increasingly difficult towards the end of the study because of the move towards day-stay surgery.

Overnight pulse oximetry did not differ between the groups. Fewer patients completed this part of the study because of equipment difficulties, failure of compliance during wakeful periods in the night and refusal by some children to sleep with the soft probe attached to a finger. Signal quality was frequently impaired in several cases by motion.

References

1. Austin JB, Russell G, Adam MG, Mackintosh D, Kelsey S, Peck DF. Prevalence of asthma and wheeze in the Highlands of Scotland. *Archives of Disease in Childhood* 1994; **71**: 211–216.
2. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalational anesthesia on airways. *Anesthesiology* 1982; **56**: 107–111.
3. Pasch T, Kamp H-D, Petermann H. Die Wirkung von Halothan, Enfluran, und Isofluran auf Resistance und Compliance bei Patienten mit Asthma oder chronischobstructiven Lungenerkrankungen. *Anaesthetist* 1991; **40**: 65–71.
4. Heneghan CPH, Bergman NA, Jordan C, Lehane JR, Catley DM. Effect of isoflurane on bronchomotor tone in man. *British Journal of Anaesthesia* 1986; **58**: 24–28.
5. Schwartz S. Treatment of status asthmaticus with halothane. *Journal of the American Medical Association* 1984; **251**: 2688.
6. Raine J, Palazzo M, Kerr JH, Sleight P. Near-fatal bronchospasm after oral nadolol in a young asthmatic and response to ventilation with halothane. *British Medical Journal* 1981; **282**: 548.
7. Vettermann J, Beck KC, Lindahl SGE, Brichant J-F, Rehder K. Actions of enflurane, isoflurane, vecuronium, atracurium, and pancuronium on pulmonary resistance in dogs. *Anesthesiology* 1988; **69**: 688–695.
8. Polgar G, Promadhat V. *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia: Saunders, 1971.
9. West JB. *Respiratory Physiology—The Essentials*. Baltimore: Williams and Wilkins, 1990.

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Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children†

J.-M. MALINOVSKY, F. SERVIN, A. COZIAN, J.-Y. LEPAGE AND M. PINAUD

Summary

It has been suggested that nasal administration of ketamine may be used to induce anaesthesia in paediatric patients. We have examined the pharmacokinetics of ketamine and norketamine after nasal administration compared with rectal and i.v. administration in young children. During halothane anaesthesia, 32 children, aged 2–9 yr, weight 10–30 kg, were allocated randomly to receive ketamine 3 mg kg^{-1} nasally (group IN3) or ketamine 9 mg kg^{-1} nasally (group IN9); ketamine 9 mg kg^{-1} rectally (group IR9); or ketamine 3 mg kg^{-1} i.v. (group IV3). Venous blood samples were obtained before and up to 360 min after administration of ketamine. Plasma concentrations of ketamine and norketamine were measured by gas liquid chromatography. Statistical comparisons were performed using ANOVA and the Kruskall–Wallis test, with $P < 0.05$ as significant. Mean plasma concentrations of ketamine peaked at 496 ng ml^{-1} in group IN3 within 20 min, 2104 ng ml^{-1} in group IN9 within 21 min, and 632 ng ml^{-1} in group IR9 within 42 min. Plasma concentrations of norketamine peaked at approximately 120 min after nasal ketamine, but appeared more rapidly after rectal administration of ketamine and were always higher than ketamine concentrations in the same situation. Calculated bioavailability was 0.50 in groups IN3 and IN9 and 0.25 in group IR9. We conclude that nasal administration of low doses of ketamine produced plasma concentrations associated with analgesia, but using high doses via the nasal route produced high plasma concentrations of ketamine similar to those that induce anaesthesia. However, the large volume of ketamine required was partly swallowed and led to an unacceptable variability of effect that precludes this route for induction of anaesthesia. (*Br. J. Anaesth.* 1996; **77**: 203–207)

Key words

Anaesthesia, paediatrics. Anaesthetic techniques, i.v. Anaesthetic techniques, rectal. Anaesthetic techniques, nasal. Pharmacokinetics, ketamine. Premedication, ketamine. Anaesthetics i.v., ketamine.

Although psychic emergence phenomena from ketamine anaesthesia restrict its use in paediatric patients [1], it may be used with premedication (i.e. midazolam) which prevents these phenomena [2] when administered first. The original agent remains popular for induction of anaesthesia in young children as it can be given as the sole anaesthetic agent and by alternative non-invasive routes such as rectally [3, 4].

Previous studies have reported its use by the oral and nasal routes. After oral ketamine 6 mg kg^{-1}, approximately 25 % of a paediatric population appeared asleep or barely arousable within 10 min [5]. The nasal route has been investigated for midazolam [6] or opioid [7] premedication and it has been tested with ketamine as an adjunct for induction of anaesthesia [8]. Loss of responsiveness occurred within 3–10 min in 35 % of children after one to three 3-mg kg^{-1} nasal ketamine doses [8]. This suggests that nasal administration of ketamine might be used for induction of anaesthesia.

Ketamine pharmacokinetics have been described after i.v. [9], i.m. [10], oral [10] and rectal [4] administration, but not after nasal administration. In this study we have determined and compared the pharmacokinetics of ketamine and its main metabolite, norketamine, when administered by nasal, rectal and i.v. routes in healthy anaesthetized children.

Patients and methods

After obtaining institutional approval and written informed consent from parents, we studied 32 ASA I boys, 2–9 yr of age, weighing 10–30 kg, undergoing minor urological surgery. Exclusion criterion included: rhinopharyngitis, digestive disorders, treatment with theophylline, H_2 receptor antagonists, β-lactamines associated with clavulanic acid and aminoglycosides, and an anaesthetic procedure involving barbiturate administration.

Anaesthesia was induced with halothane (2 MAC) and 50 % nitrous oxide in oxygen via a face mask. Anaesthesia was maintained with halothane for induction of anaesthesia (1 MAC and during ketamine administration) without tracheal intu-

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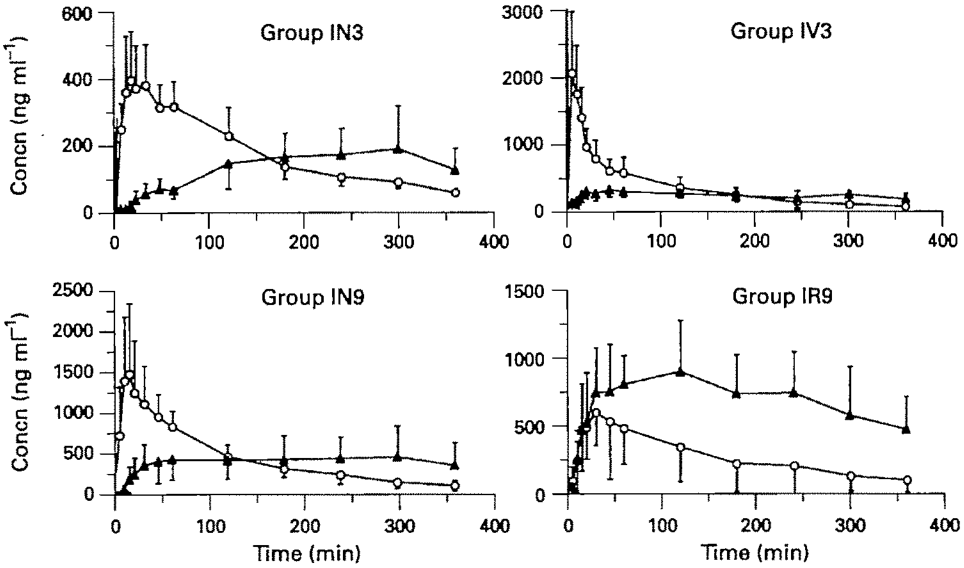

Figure 1 Mean concentration–*vs*–time curves (mean, SD) of ketamine (○) and norketamine (▲) in the different groups receiving ketamine i.v., nasally (IN) and rectally (IR).

bation. After cannulation of a vein on the forearm using a short 20-gauge catheter and i.v. injection of atropine 15 μg kg^{-1}, children were allocated randomly to one of four groups to receive 5% ketamine (Parke Davis Lab.) as follows: group IN3 ($n = 8$) received ketamine 3 mg kg^{-1} nasally; group IN9 ($n = 8$) ketamine 9 mg kg^{-1} nasally; group IV3 ($n = 8$) ketamine 3 mg kg^{-1} i.v.; and group IR9 ($n = 8$) ketamine 9 mg kg^{-1} rectally. In groups IN, half of the indicated dose was administered in each nostril within 15 s. All children received an enema 1 h before anaesthesia and rectal administration was performed via a short air-washed cannula. After i.v. administration, the venous catheter was flushed with physiological saline 10 ml. In all groups, heart rate and pulse oximetry were monitored continuously, and non-invasive arterial pressure and ventilatory frequency recorded at regular intervals during anaesthesia. Administration of halothane was stopped 15 min after administration of ketamine in all children. Time elapsed between ketamine administration and complete recovery from anaesthesia (when the child was able to open his eyes and answer correctly to verbal command) was recorded. Doses and time of analgesic requests during the postoperative period were noted.

Thirteen 5-ml venous blood samples were obtained before and 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300 and 360 min after administration of ketamine. Plasma was separated by centrifugation and stored at −20 °C until analysis. Plasma concentrations of ketamine and its major metabolite, norketamine, were measured by gas–liquid chromatography (supplied by Parke-Davis-France). The internal standard was diphenhydramine 5 μg ml^{-1}. The calibration curves for ketamine and norketamine were linear within the range 0–2000 ng ml^{-1}. Greater concentrations required dilution of plasma samples before extraction. The standard variations for ketamine and norketamine were, respectively, 4.4% and 6.9% for 20 ng ml^{-1}, and 1.7% and 3.4% for 2000 ng ml^{-1}.

Pharmacokinetic variables were calculated by conventional means from plasma concentration–*vs*–time data. Ketamine and norketamine concentration–*vs*–time curves obtained for individual patients were fitted to the sum of exponential functions derived from Colburn [11] and interpreted as one- or two-compartment models. Pharmacokinetic data were fitted using the Siphar program [12], with a weighing function of $1/y^2$. The quality of fit of the two-compartment model was assessed by the presence of a random scatter of data around a calculated value [13], and by visual assessment of the residuals of the observed values from the fitted curve. After modelling, the rate constant for elimination (k_e) was obtained, and the elimination half-life ($T_{1/2}$) was calculated as (0.693 k_e). The area under the plasma concentration curve from 5 to 360 min (AUC$_{5-360}$) was calculated by the trapezoidal rule and was extrapolated from the origin to infinity (AUC$_{0-\infty}$) from the k_{abs} and k_n slopes. Clearance was calculated using the formula: Cl = dose/AUC. Analysis from the extrapolated area allowed estimation of steady state volume of distribution (V^{ss}). Availability (F) for the different routes was calculated after children were paired between each non-i.v. group and group IV according to weight. In each non-i.v. group, peak ketamine concentration and its time were estimated from the fitted model. Statistical comparisons were carried out using ANOVA and the Kruskall–Wallis test where appropriate; $P < 0.05$ was considered significant. Data are presented as mean (SD).

Results

Mean age and weight of the children were, respectively, 4.8 (range 2–8) yr and 18.6 (SD 2.9) kg in group IV3; 4.8 (3–9) yr and 18.4 (4.7) kg in group IN3; 3.3 (2–7) yr and 17.1 (14.9) kg in group IN9; and 4.0 (3–9) yr and 17.8 (5.7) kg in group IR9 (ns). Surgical procedures included herniorrhaphy, repair of undescended testis, circumcision or hypospadias

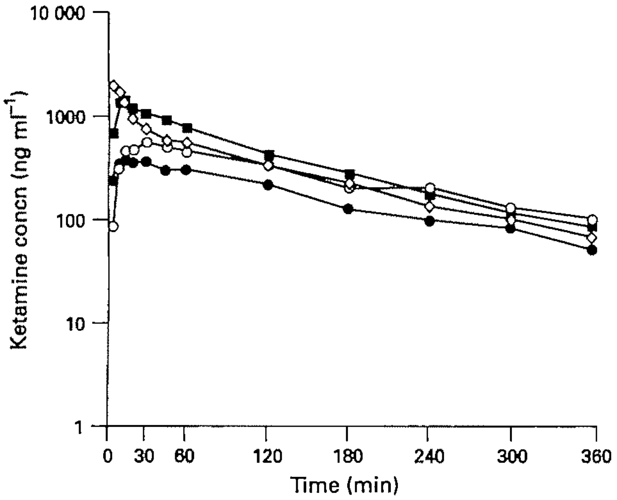

Figure 2 Logarithmic conversion of mean ketamine plasma concentration–*vs*–time curves in group IV3 (◇), group IN3 (●), group IN9 (■) and group IR9 (○).

repair. No children experienced coughing or defaecation, nasal disturbances or rectal postoperative lesions after intranasal or rectal administration of ketamine.

Mean arterial pressure and heart rate did not vary significantly from baseline values in any group during halothane anaesthesia or ketamine administration. Sp_{O_2} did not decrease except in two children who received i.v. ketamine and demonstrated a transient decrease at 88% and 89% from baseline values of 98%; these children had plasma ketamine concentrations greater than 2000 ng ml^{-1} at 5 and 10 min after administration of ketamine. Assisted ventilation via a face mask was used temporarily (less than 5 min) in these patients. Ventilatory frequency did not vary in groups IN3 and IR9, but increased significantly at 5 min in group IV3 and at 10 min in group IN9 (+34 (12)% and 46 (21)%, respectively). No additional analgesia was required in any group during surgery or during the 6 h after operation. Complete recovery from anaesthesia was delayed in group IN9 (107 (23) min) compared with the other groups: group IN3, 72 (15) min; group IR9, 57 (11) min; and group IV3, 63 (16) min ($P < 0.01$).

Because of blood sampling difficulties, two children were excluded from pharmacokinetic analysis (one in group IN9 and another in group IR9). Mean ketamine and norketamine plasma concentration–*vs*–time curves for each group are shown in figure 1. Logarithmic conversion of mean plasma concentration–*vs*–time curves for ketamine in each group are presented in figure 2. Individual $C_p$max and tC_pmax values for ketamine in the different groups are shown in table 1. Pharmacokinetic variables are summarized in table 2. After pairing children according to weight and age, estimated bioavailabilities were, respectively, 0.50 (0.19) after nasal ketamine 3 mg kg^{-1} and 0.50 (0.27) after 9 mg kg^{-1}, and 0.25 (0.19) after ketamine 9 mg kg^{-1} rectally.

Discussion

We have found that the same dose of ketamine (9 mg kg^{-1}) induced more rapid and greater plasma concentrations after nasal than after rectal administration, but that the rectal route was associated with earlier appearance of norketamine because of first-pass metabolism.

The doses used in our study were those that induced general anaesthesia by the i.v. and rectal

Table 1 Individual calculated $C_p$max and tC_pmax values for ketamine from a fitted model (mean (SD)) in group IV3 (ketamine 3 mg kg^{-1} i.v.), group IN3 (ketamine 3 mg kg^{-1} intranasally), group IN9 (ketamine 9 mg kg^{-1} intranasally) and group IR9 (ketamine 9 mg kg^{-1} rectally). Kruskal–Wallis test: $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* group IN9.

	Group					
	IN3		IN9		IR9	
Children No.	$C_p$max (ng ml^{-1})	tC_pmax (min)	$C_p$max (ng ml^{-1})	tC_pmax (min)	$C_p$max (ng ml^{-1})	tC_pmax (min)
1	1020	9	2807	18	537	34
2	288	13	1395	9	414	64
3	267	34	2393	9	742	27
4	287	27	1500	19	583	18
5	556	19	561	37	455	30
6	305	23	3129	44	316	54
7	683	15	2944	11	1380	66
8	558	18	—	—	—	—
Mean	496***	20	2104	21	632**	42
SD	266	8	965	14	356	19

Table 2 Pharmacokinetic variables of ketamine after the different routes of administration (mean (SD)). Kruskall–Wallis test: $^{*}P < 0.05$, $^{**}P < 0.01$ *vs* group IV3; $^{\dagger\dagger}P < 0.001$ *vs* other routes of administration

Group	$T_{1/2}$ (min)	V^{ss} (litre kg^{-1})	Cl (ml min^{-1} kg^{-1})	AUC$_{0-\infty}$ (mg ml^{-1} min^{-1})
IN3 ($n = 8$)	123 (35)	8.5 (2.7)*	49.9 (20.2)	76.4 (28.2)††
IN9 ($n = 7$)	120 (34)	8.3 (3.2)*	59.7 (19.5)	163.6 (64.5)
IR9 ($n = 7$)	100 (28)	18.1 (9.0)**	121.5 (74.8)**	111.2 (85.5)
IV3 ($n = 8$)	125 (46)	2.8 (1.2)	22.0 (9.8)	148.3 (55.0)

Table 3 Comparative data published previously on the pharmacokinetic variables of ketamine in adults and children. F = Bioavailability after non-i.v. administration of ketamine. A = Adults; C = children; * unpremedicated patients; i.r. = rectal administration; i.v. = i.v. injection; i.m. = i.m. administration; NR = not reported

Author		Route	Dose of ketamine (mg kg^{-1})	F	$T_{\frac{1}{2}}^{\beta}$ (min)	V^{ss} (litre kg^{-1})	Cl (ml kg^{-1} min^{-1})
Wieber [21]	A	i.v.	2.5		151		
Domino [20]	A	i.v.	2.2		144	1.5	14
		i.v.*	2.2		135	1.8	12
Domino [23]	A	i.v.	2.2		158	3.2	28
Grant [9]	A	i.v.	2.0		153	2.3	13
Grant [10]	A	i.m.	0.5	93	155		
	A	oral	0.5	17	200		
Clements & Nimmo [22]	A	i.v.	0.125		≈ 180	2.1	16
	A	i.v.	0.250		≈ 180	3.1	19
Grant [9]	C	i.v.	2.0		103	1.9	17
	C	i.m.	6.0	NR	100		
Idvall [4]	C	i.r.	9.0	NR	109		
Present study	C	i.v.	3.0		125	2.8	22
	C	i.n.	3.0–9.0	50	122		
	C	i.r.	9.0	25	100		

routes, and for the nasal route were those reported as effective in a previous study [8]. However, a relationship with clinical effects may not be established as sampling occurred during general anaesthesia. Moreover, it may be noted that the volumes administered nasally in group IN9 were large and probably unacceptable in a conscious, unpremedicated child.

There are several problems in the pharmacokinetic interpretation of the data obtained after different models of administration of ketamine as children were not their own controls. However, such comparisons between non-i.v. and i.v. administrations of anaesthetic agents are frequently made in children who are not their own controls [14–16]. Therefore, in order to obtain a meaningful analysis, children were paired accordingly to age and weight between non-i.v. and i.v. groups for estimation of ketamine bioavailability. Furthermore, to facilitate venous access and blood sampling, ketamine was administered during general anaesthesia to ensure maintenance of anaesthesia and postoperative analgesia as a result of generation of norketamine which is a potent analgesic drug [10]. Such a study design is seldom used but ketamine associated with propofol has been proposed for ambulatory surgery [17]. Our study did not allow pharmacokinetic analysis of norketamine because the sampling period could not be extended further than 6 h in those children treated on a day-case hospital stay basis.

Ketamine metabolism is dependent on hepatic blood flow and could therefore be influenced by co-administered drugs, for example halothane. Halothane induces a marked decrease in hepatic blood flow, reduces intrinsic drug metabolism capacity [18] and diminishes ketamine clearance [19]. Its use could therefore enhance ketamine plasma concentrations and delay norketamine generation. However, all children exhibited a similar haemodynamic state when they received the same dose of halothane, and therefore the influence of halothane on hepatic blood flow was probably the same in all children.

The pharmacokinetic variables after i.v. ketamine were similar to those reported previously in adult patients or children [9, 20–24] and are summarized in table 3. The volume of distribution of approximately 3 litre kg^{-1} reflects the high liposolubility of ketamine and a high clearance (22 ml kg^{-1} min^{-1}) accounts for the relatively short elimination half-life. As described previously the appearance of norketamine was delayed which suggests that norketamine plays a role in the clinical duration of action of ketamine. In all children, plasma concentrations of norketamine 6 h after administration of i.v. ketamine were greater than 150 ng ml^{-1}, the threshold for analgesia reported previously [10].

The amount of ketamine which reached the systemic circulation was reduced with the non-i.v. routes. The bioavailability of ketamine in the absence of a first-pass hepatic effect, as observed via the nasal route, was approximately twice that observed via the rectal route. Certainly, ketamine administration during general anaesthesia leads to maximal mucosal absorption of the drug, proportional to the dose administered, with an early plasma peak in both nasal groups. Plasma ketamine concentrations in group IN9 were consistent most of the time with those associated with induction of anaesthesia. However, general anaesthesia and the supine position avoided expulsion of part of the dose from sneezing or coughing, or swallowing; however, two children receiving a large volume in group IN9 exhibited plasma concentration decay curves consistent with digestive absorption of the drug. Nevertheless, the amount of drug required with the current formulation of ketamine implies that intranasal administration of a large volume of solution which would probably be swallowed by a conscious child would be even more than that observed in this study. This leads to an unacceptable variability of effect which precludes the use of this route for induction of anaesthesia.

After rectal administration, ketamine absorption was delayed and interindividual variations were large. Despite the fact that every child in this group received a rectal enema before induction of anaesthesia, rectal evacuation was never certain, and the differences in rectal pH values of children [24] might modify drug absorption. As described previously [4], norketamine generation was rapid in this group, because of first-pass metabolism. These early high plasma norketamine concentrations may participate in the anaesthetic action of ketamine in this situation, and partly compensate for low bioavailability. This low bioavailability is similar to that described after oral administration of ketamine [9].

References

1. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56**: 119–136.
2. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaesthesia. *Anaesthesia* 1984; **59**: 439–442.
3. Saint-Maurice, Laguenie G, Couturier C, Goutail-Flaud F. Rectal ketamine in pædiatric anaesthesia. *British Journal of Anaesthesia* 1979; **51**: 573–574.
4. Idvall J, Holasek J, Stenberg P. Rectal ketamine for induction of anaesthesia in children. *Anaesthesia* 1983; **38**: 60–64.
5. Gutstein HW, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; **76**: 28–33.
6. Wilton NC, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988; **69**: 972–975.
7. Henderson JM, Drodsky DA, Fischer DM, Brett CM, Hertzka RE. Pre-induction of anesthesia in pediatric patients with nasally administered sufentanil. *Anesthesiology* 1988; **68**: 671–675.
8. Aldrete JA, Roman-de Jesus JC, Russell LJ, D'Cruz O. Intranasal ketamine as induction adjunct in children: preliminary report (abstract). *Anesthesiology* 1987; **67**: A514.
9. Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. *British Journal of Anaesthesia* 1983; **55**: 1107–1111.
10. Grant IS, Nimmo WS, Clements JA. Pharmacokinetic analgesic effects of i.m. and oral ketamine. *British Journal of Anaesthesia* 1981; **53**: 805–810.
11. Colburn WA. Simultaneous pharmacokinetics and pharmacodynamic modeling. *Journal of Pharmacokinetics and Biopharmaceutics* 1984; **12**: 545–548.
12. Gomeni R. PHARM—an interactive graphic program for individual and population pharmacokinetic parameter estimation. *Computers in Biology and Medicine* 1984; **14**: 25–34.
13. Berman M, Shahn E, Weiss MF. The routine fitting of kinetic data to models: A mathematical formalism for digital computers. *Biophysical Journal* 1962; **2**: 275–287.
14. Payne K, Mattheyse FJ, Liebenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. *European Journal of Clinical Pharmacology* 1989; **37**: 267–272.
15. Rey E, Delaunay L, Murat I, Richard MO, Saint-Maurice C, Olive G. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *European Journal of Clinical Pharmacology* 1991; **41**: 355–357.
16. Malinovsky JM, Lejus C, Servin F, Lepage JY, Le Normand Y, Testa S, Cozian A, Pinaud M. Midazolam plasma concentrations after intravenous, intranasal or intrarectal administration in children. *British Journal of Anaesthesia* 1993; **70**: 617–620.
17. Guit JBM, Koning HM, Coster ML, Niemeijer RPE, Mackie DP. Ketamine as analgesic for total intravenous anaesthesia with propofol. *Anaesthesia* 1991; **46**: 24–27.
18. Reilly CS, Wood AJJ, Koshi RP, Wood M. The effect of halothane on drug disposition: contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. *Anesthesiology* 1985; **63**: 70–76.
19. White PF, Marietta MP, Pudwill CR, Way WL, Trevor AJ. Effects of halothane anaesthesia on the biodisposition of ketamine in rats. *Journal of Pharmacology and Experimental Therapeutics* 1976; **196**: 545–555.
20. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, Zsigmond EK. Ketamine kinetics in unpremedicated and diazepam-premedicated subjects. *Clinical Pharmacology and Therapeutics* 1984; **36**: 645–653.
21. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. *Anaesthetist* 1975; **24**: 260–263.
22. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *British Journal of Anaesthesia* 1981; **53**: 27–30.
23. Domino EF, Zsigmond EK, Domino LE, Domino KE, Kothary SP, Domino SE. Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay. *Anesthesia and Analgesia* 1982; **61**: 87–92.
24. Jantzen JP, Tzanova I, Witton PK, Klein AM. Rectal pH in children. *Canadian Journal of Anaesthesia* 1989; **36**: 665–667.

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Determinants of duration of ICU stay after coronary artery bypass graft surgery

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and S. Geroulanos

Summary

Prediction of duration of a patient's stay in the ICU after cardiac surgery is difficult. In 652 consecutive adult patients undergoing elective coronary artery bypass graft (CABG) surgery, we analysed prospectively preoperative and immediate postoperative variables thought to influence duration of stay in the ICU. With univariate analysis, we found that age, preoperative left ventricular ejection fraction, bypass time, aortic cross-clamp time, blood transfusions and the number of inotropic agents administered in the immediate postoperative period (for at least 6 h) were significant correlates of duration of stay in the ICU. However, logistic regression analysis showed that the number of inotropes was the most important determinant of stay in the ICU, with an overall prediction accuracy of 94.8%. The main cause of prolonged stay in the ICU (more than 2 days) was low cardiac output syndrome. We conclude that analysis of perioperative variables enhanced our ability to accurately predict duration of stay in the ICU in cardiac surgery patients. The number of inotropic agents administered during the first 6 h after operation was the most important determinant of duration of stay in the ICU. (*Br. J. Anaesth.* 1996; 77: 208–212)

Key words
Surgery, cardiovascular. Intensive care. Heart, coronary artery bypass. Risk.

Despite recent efforts to bypass intensive care unit (ICU) stay [1], cardiac surgery patients are invariably monitored in the ICU for a period of time that varies from 1 to several days. Prolonged stay in the ICU not only increases the overall costs of cardiac surgery, but it may also limit the number of operations performed. Therefore, the ability to accurately predict the duration of stay in the ICU and patient outcome is important.

The scoring systems used to predict a patient's stay in a general ICU have not been found to be useful in the postoperative cardiac ICU [2, 3]. Over the past few years, attempts have been made to develop predictive models of stay in the ICU with special applicability to cardiac surgery patients. However, the majority of reported models are complex, impractical for intercentre use and of modest predictive ability [4–6]. This may result partly from the fact that all studies analysed preoperative variables and ignored variables related to the operation itself.

In this study, we have assessed determinants of length of stay in the ICU in postoperative coronary artery bypass graft (CABG) surgery patients by analysing both preoperative and immediate postoperative variables. This approach has enabled us to develop a simple and more accurate predictive index of stay in the ICU.

Patients and methods

From January 1994 to December 1994, we studied prospectively 652 consecutive patients undergoing elective CABG surgery in our hospital. We recorded patients variables, New York Heart Association (NYHA) class and preoperative left ventricular ejection fraction assessed by angiography (grade 1 > 50%; grade 2 35–50%; grade 3 20–34%; and grade 4 < 20%).

We also recorded the type of cardioplegia used, number of grafts, aortic cross-clamp time and bypass time. In addition, we recorded the number of inotropic drugs administered during the first 6 h in the ICU. Collection of these data in no way interfered with or affected the care of patients being studied; therefore, it was deemed that patient consent was not required. Approval for this study was obtained from the Ethics and Research Committee for our institution.

Inotropic drugs were used to treat low cardiac output syndrome, defined as a cardiac index < 2 litre min^{-1} m^{-2}, despite optimal filling pressures (wedge pressure 12 mm Hg). Inotropes were included only if they were given in the ICU for at least 6 h, immediately after surgery. In this situation, dobutamine, adrenaline or dopamine, up to maximum doses (adrenaline 2 μg kg^{-1} min^{-1}, dobutamine 20 μg kg^{-1} min^{-1} or dopamine 20 μg kg^{-1} min^{-1}) were

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Table 1 Patient data (mean (range) or number (%)) ($n = 652$)

	n	(%)
Sex (M/F)	592/60	90.8/9.2
Age (yr)	62.1 (31–81)	
Smokers	443	67.9
Left ventricular ejection fraction		
Grade 1 (> 50%)	182	27.9
Grade 2 (35–50%)	331	50.7
Grade 3 (20–34%)	121	18.5
Grade 4 (< 20%)	18	2.8
NYHA classification system		
Class I	221	33.9
Class II	205	31.4
Class III	130	19.9
Class IV	96	14.7

usually used initially. If there was need for additional inotropic support (persistence of condition) within this critical period, milrinone or noradrenaline ($1\ \mu g\ kg^{-1}\ min^{-1}$ or $0.3\ \mu g\ kg^{-1}\ min^{-1}$, respectively) were then added [7]. Dopamine at renal doses was excluded. The amount of blood transfused in the operating room and during the first 6 h after operation was also recorded. Blood transfusion was given when the patient's packed cell volume (PCV) was < 27%.

Duration of mechanical ventilation, all postoperative complications, duration of stay in the ICU and patient outcome were recorded for all patients. For this analysis, prolonged stay in the ICU was defined as greater than 2 days. No patient was excluded. Patient outcome was evaluated on the day of ICU discharge.

Data were analysed using BMDP statistical software (Los Angeles, CA, USA) [8]. Continuous variables were analysed using the two-sample *t* test. The chi-square test was used for discrete variables. To assess the ability of independent variables to predict a dependent variable, the odds ratio was calculated [9]. Furthermore, the data were subjected to logistic regression analysis where ICU duration constituted the binary dependent variable (2 *vs* > 2 days). Sex and cardioplegia (crystalloid *vs* blood) were categorical predictors, and ejection fraction, aortic cross-clamp time, bypass time, number of grafts, units of blood transfused and number of inotropic drugs administered were interval-scaled predictors. The fit of the model was assessed by the Hosmer–Lemeshow goodness-of-fit statistic [10]. Data are reported as the mean (SD) and were considered significant when $P < 0.05$.

Results

Patient characteristics and preoperative data are shown in table 1. For all patients, mean duration of stay in the ICU was 2.3 (SD 1.6) days (range 0.75–62 days) and duration of mechanical ventilation 0.8 (0.3) days. Of all patients, 585 patients (89.7%) were discharged in less than 2 days (group A), whereas 67 patients (10.3%) remained in the ICU for more than 2 days (group B). Patient characteristics and differences in perioperative variables for both groups are presented in table 2. The two groups did not differ in sex distribution, cardioplegia, preoperative haemoglobin (PCV) or number of grafts. Ejection fraction was a significant predictor of prolonged stay in the ICU ($P < 0.001$). Use of inotropes was also associated with prolonged stay in the ICU. For example, use of one inotrope was associated with an odds ratio of 2, and use of two inotropes with an odds ratio of 104 ($P < 0.0001$). Aortic cross-clamp time in excess of 90 min was associated with a statistically significant and sharp increase in odds ratio for prolonged stay in the ICU ($P < 0.001$). Bypass time longer than 120 min increased the risk for prolonged stay in the ICU, corresponding to an odds ratio of 4.3 ($P < 0.001$). There was a non-monotonic relation of risk for prolonged stay in the ICU and the amount of blood transfused; patients who received more than 6 u. of blood were at a substantially increased risk for prolonged stay in the ICU (odds ratio 13.5; $P < 0.001$).

Table 3 shows the results of a forward stepwise selection of variables into the logistic model. Five variables were entered based on their statistical significance (entering criterion $P < 0.15$). A backward selection procedure led to the same set of five variables in the model (removing criterion $P > 0.20$). The great majority of improvement in this model fit

Table 2 Patient characteristics and perioperative variables in patients with short (≤ 2 days) (group A) or long (> 2 days) (group B) ICU stay (mean (SD or range) or number (%))

	Group A		Group B		
	n	(%)	*n*	(%)	*P*
No. of patients	585	89.7	67	10.3	
Sex (M/F)	531/54	90.8/9.2	61/6	91.0/9.0	0.5
Age (yr)	61.7 (31–81)		66.1 (47–79)		0.001
Ejection fraction (%)	0.46 (0.1)		0.34 (0.07)		0.000
Aortic cross-clamp time (min)	54 (17)		70 (19)		0.000
Bypass time (min)	94 (28)		131 (44)		0.000
Type of cardioplegia					
Blood	308	52.6	37	55.2	0.7
Crystalloid	277	47.4	30	44.8	
Blood units transfused	4.2 (1.7)		7.5 (2.5)		0.000
Inotropes					0.000
Yes	167	28.5	60	89.6	
No	418	71.5	7	10.4	
Grafts					0.6
≤ 2	286	48.9	30	44.8	
≥ 3	299	51.1	37	55.2	

Table 3 Summary of stepwise selection results

Step	df	Log likelihood	Improvement chi-square (df = 1)	*P*	Goodness of fit (Hosmer–Lemeshow)	
					Chi-square (df)	*P*
0	1	−218.04				
1. Inotropes	1	−114.87	188,328	0.000	21.72 (8)	0.0055
2. Blood units	1	−85.88	15,661	0.000	23.06 (8)	0.0033
3. Ejection fraction	1	−63.12	8,204	0.000	24.22 (8)	0.0021
4. Age	1	−58.88	13,123	0.004	11.66 (8)	0.1671
5. Cardioplegia	1	−56.11	8,613	0.019	12.38 (8)	0.1349

Table 4 Number of patients (%) in ICU groups as a function of number of inotropes used

	Inotropes			
	0	1	2	3
≤ 2 days	418 (98.3)	147 (96.7)	19 (31.1)	1 (7.1)
> 2 days	7 (1.7)	5 (3.3)	42 (68.9)	13 (92.9)
Total	425 (100)	152 (100)	61 (100)	14 (100)

Table 5 Number of patients (%) in ICU groups as a function of inotrope groups used

	Inotropes		
	0 or 1	≥ 2	Total
≤ 2 days	564 (96.4)	21 (3.6)	585 (100)
> 2 days	13 (19.4)	54 (80.6)	67 (100)

was associated with the number of inotropes used, the number of blood units and preoperative ejection fraction.

Table 4 shows the number and percentage of patients in each ICU stay-group for the four levels of inotropes observed. Using inotropes as a binary predictor, with values of 0 and 1 indicating stay in the ICU of 2 days or less, and 2 or more indicating more than 2 days, the overall prediction accuracy was 95.1 % (620 of 652) based on 96.6 % for predicting short stays (565 of 585) and 82.1 % for long stays (55 of 67) (table 5). These rates are close to the five predictor model of table 3 and also to a five predictor model where the binary inotropes variable itself was substituted for the interval variable. Thus the binary inotropes variable is an accurate and simple predictor of stay in the ICU.

The causes resulting in prolonged stay in the ICU were low cardiac output syndrome in 35 (52.2 %), respiratory failure in eight (11.9 %), neuro-psychiatric abnormalities in five (7.5 %) and combination of the above in 19 (28.3 %) patients. For both groups, mean duration of mechanical ventilation, ICU and hospital stay, and mortality rate are presented in table 6. The overall ICU mortality rate was 0.8 %.

Causes for a longer stay in the ICU for the group receiving less than two inotropes ($n = 13$) were hypoxaemia ($n = 6$), atrial fibrillation ($n = 3$), their combination ($n = 3$) and mental disturbances ($n = 1$).

Discussion

This study included both preoperative and immediate postoperative variables in a logistic regression model and developed an index to predict duration of stay in the ICU after cardiac surgery. We found that patients who had a low ejection fraction, had received a large number of units of blood or more than one inotropic agent remained in the ICU for a longer period than usual. Sex, bypass time, aortic cross-clamp time and number of grafts were not significant predictors. Among all variables examined, the number of inotropic drugs administered in the immediate postoperative period was the most reliable predictor of stay in the ICU, with an overall predictive accuracy of 94.8 %. This is supported by our finding that the most frequent cause of prolonged stay in the ICU was low cardiac output syndrome; however, it should be noted that the number of inotropes rather than inotrope use was the significant factor.

The major limitation of this study was that this index was derived after the patient's stay in the ICU for 6 h. In this sense, it cannot be used as a preoperative prognostic indicator of duration of stay in the ICU. In our study, there was a delay of a few hours for predicting the duration of stay in the ICU, but we believe that there is still considerable value in predicting the length of stay in the intensive care unit in the early postoperative period. The accuracy

Table 6 Duration of mechanical ventilatory support, ICU and hospital stay, and mortality rate for both groups (mean (SD))

	Group A (ICU stay ≤ 2 days)	Group B (ICU stay > 2 days)	*P*
Mech. ventilation (days)	0.5 (0.05)	3.8 (1.4)	0.001
ICU stay (days)	1.3 (0.3)	7 (4.5)	0.001
Hospital stay (days)	7.1 (0.8)	14.6 (3.9)	0.001
ICU mortality	0.3 %	4.5 %	0.0001

of our prediction was much higher compared with similar, previous studies which used only preoperative variables. The determinants of this study can be considered similar to the APACHE II scoring system, which predicts patient outcome at the time of admission to the ICU, but has a poor performance in cardiac surgery patients [11].

Over the past 5 yr, several studies have developed predictive indices of stay in the ICU after cardiac surgery. The majority of these studies have included preoperative variables and, in general, have not taken into account events that affect patient outcome during the operative or immediate postoperative period. A great disparity in type and number of independent variables analysed has been reported. Tuman and co-workers [4] found 11 variables to be significantly associated with stay in the ICU, including emergency surgery, age, preoperative renal dysfunction, previous myocardial infarction, cerebrovascular disease, type of surgery, congestive heart failure and left ventricular dysfunction. Although the duration of stay in the ICU in this study correlated with a clinical risk score derived from these variables, no accurate predictive index of stay in the ICU based on clinical score was provided. Furthermore, it cannot be determined which risk factor is the most significant predictor of length of stay in the ICU.

In a similar study of preoperative variables, Tu and co-workers [12] suggested that length of stay in the ICU after cardiac surgery could be predicted by a multivariate predictive index. Five variables were found to be statistically significant independent predictors for a prolonged stay in the ICU (age, female sex, left ventricular function, urgency of surgery and type of surgery). A predictive index was developed for length of stay in the ICU with a risk score of 0–12. Patients with a low risk score remained in the ICU for a few days, while patients with a high risk score had a prolonged stay in the ICU. However, this model has a poor predictive ability; 31.7% of patients with a low risk score (0–3) stayed more than 2 days stay in the ICU, whereas only 69.4% of patients with a high risk score (> 8) had a prolonged (> 2 days) stay in the ICU. The authors acknowledged that length of stay in the ICU can never be predicted with certainty.

One year later, Tu, Jaglal and Naylor [13] reported that duration of stay in the ICU after cardiac surgery could be predicted using a six-variable risk index which included age, sex, preoperative ejection fraction, type of surgery, urgency of surgery and reoperation. Although the authors considered prolonged stay in the ICU as longer than 6 days, the overall predictive ability of their index was poor (67%).

The fundamental difference between our study and those described above is that we took into account not only preoperative variables, but also significant variables related to both the operative and immediate postoperative period, such as number of inotropes administered and blood transfusions. We found that duration of stay in the ICU depended predominantly on a single critical variable, number of inotropes administered during the immediate postoperative period. This is not surprising because inotropic support reflects poor cardiac function. It follows that the group requiring intensive inotropic support would include patients with intraoperative complications (e.g. myocardial ischaemia or infarction), inadequate revascularization, low cardiac output syndrome related to systemic inflammatory response syndrome (SIRS), stunned myocardium or inadequate myocardial protection during bypass. Apparently, none of these conditions can be predicted accurately by any preoperative variable. On the other hand, in some high-risk cases (e.g. low ejection fraction) there may be great improvement in left ventricular function after operation as a result of successful revascularization. This is supported by the study of Zaroff and colleagues who found that, although low preoperative ejection fraction is a known predictor of poor immediate postoperative outcome after cardiac surgery, not all patients with low preoperative ejection fraction required inotropic support [14]. In both cases, the models based on preoperative variables are likely to fail in predicting stay in the ICU.

Our findings are in agreement with those reported by Weintraub and co-workers [15], who showed that the correlates of prolonged hospital stay could not be predicted by preoperative variables alone. The authors emphasized that serious complications were responsible for prolonging the length of stay after coronary artery bypass grafting surgery.

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References

1. Chong JL, Pillai R, Fisher A, Grebenik C, Sinclair M, Westaby S. Cardiac surgery: moving away from intensive care. *British Heart Journal* 1992; **68**: 430–433.
2. Hadorn D. Who really needs to be in the intensive care unit: Using clinical guidelines to define healthcare needs. *Critical Care Medicine* 1994; **22**: 1679–1682.
3. Green J, Wintfeld N, Sharkey P, Passman LJ. The importance of severity of illness in assessing hospital mortality. *Journal of the American Medical Association* 1990; **263**: 241–246.
4. Tuman K, McCarthy R, March R, Najafi H, Ivankovich A. Morbidity and duration of ICU stay after cardiac surgery. A model for preoperative risk assessment. *Chest* 1992; **102**: 36–44.
5. Geraci JM, Rosen AK, Ash AS, McNiff KJ, Moskowitz MA. Predicting the occurrence of adverse events after coronary artery bypass surgery. *Annals of Internal Medicine* 1993; **118**: 18–24.
6. Tu JV, Guerriere MR. Use of a neural network as a predictive instrument for length of stay in the intensive care unit following cardiac surgery. *Proceedings of the Annual Conference on Computer Applied Medical Care* 1992; **5**: 666–672.
7. Trujillo M, Arai K, Bellorin-Font E. Practical guide for drug administration by intravenous infusion in intensive care units. *Critical Care Medicine* 1994; **22**: 1049–1063.
8. Dixon WJ. *BMDP Statistical Software Manual.* Berkeley, CA: University of California Press, 1990.
9. Dawson-Saunders B, Trapp R. *Basic and Clinical Biostatistics. A Lange Medical Book*, 2nd Edn. New York: Prentice-Hall International Inc., 1994.
10. Hosmer DW, Lemeshow S. *Applied Logistic Regression.* New York: John Wiley and Sons, 1989.
11. Turner JS, Mudaliar YM, Chang RWS, Morgan CJ. Acute

physiology and chronic health evaluation (APACHE II) scoring in a cardiothoracic intensive care unit. *Critical Care Medicine* 1991; **19**: 1266–1269.

12. Tu JV, Mazer CD, Levinton C, Armstrong PW, Naylor CD. A predictive index for length of stay in the intensive care unit following cardiac surgery. *Canadian Medical Association Journal* 1994; **151**: 117–185.
13. Tu JV, Jaglal SB, Naylor CD. Multicenter validation of a risk index for mortality, intensive care unit stay, and overall hospital length of stay after cardiac surgery. *Circulation* 1995; **91**: 677–684.
14. Zaroff J, Aronson S, Lee BK, Feinstein SB, Walker R, Wiencek JG. The relationship between immediate outcome after cardiac surgery, homogeneous cardioplegia delivery and ejection fraction. *Chest* 1994; **106**: 38–45.
15. Weintraub W, Jones E, Craver J, Guyton R, Cohen C. Determinants of prolonged length of hospital stay after coronary bypass surgery. *Circulation* 1989; **80**: 276–284.

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Comparison of propofol and a propofol–methohexitone mixture for induction of day-case anaesthesia

N. THOMPSON AND G. S. ROBERTSON

Summary

We studied 99 patients undergoing day-case urological surgery, allocated randomly to receive a sleep dose of either 1% propofol or a mixture of equal volumes of 1% propofol and 0.5% methohexitone, and thereafter a standardized anaesthetic. With the exception of minor differences in intraoperative heart rate there were no significant differences between the two groups in induction properties and complications, intraoperative variables, rate of recovery or postoperative sequelae. (*Br. J. Anaesth.* 1996; **77**: 213–216)

Key words

Anaesthesia, day-case. Anaesthetics i.v., propofol. Anaesthetics i.v., methohexitone. Anaesthetic techniques, induction.

Anaesthesia for day-case surgery is designed to provide rapid, uncomplicated recovery and discharge from hospital within a few hours of surgery. Although methohexitone has previously been used commonly, propofol is now considered the induction agent of choice for day-case anaesthesia because of its short recovery time and low incidence of postoperative sequelae [1]. However, compared with methohexitone, propofol produces a greater degree of cardiovascular and respiratory depression [2] and is more expensive. A combination of these two agents might accentuate their individual advantages, while minimizing the side effects. In this study, we have compared the properties of a mixture of propofol and methohexitone with those of propofol alone for day-case anaesthesia.

Patients and methods

After approval of the local Ethics Committee, we studied 99 patients undergoing day-case urological surgery; all gave informed consent and were ASA grade I or II, aged 16–70 yr. Exclusion criteria included specific contraindications to the study drugs or halothane anaesthesia.

After recording of baseline heart rate, systolic, diastolic and mean arterial pressures (MAP), and Sp_{O_2}, a suitable vein was cannulated. Patients were then allocated randomly to one of two groups, and each patient received a sleep dose of induction agent, with the end-point defined as loss of verbal contact. For patients in group A the syringe contained 9.5 ml each of methohexitone 5 mg ml^{-1} in 0.9% sodium chloride and propofol 10 mg ml^{-1}, with 2% lignocaine 1 ml. For those in group B the syringe contained 19 ml of propofol 10 mg ml^{-1} with 2% lignocaine 1 ml. Neither investigator was aware of the patient's group, and it was not possible to differentiate visually between the contents of the syringes. All inductions and subsequent anaesthetics were carried out by one investigator (G.S.R.). The volume of agent needed to induce anaesthesia was noted, and also pain on injection, laryngeal spasm, cough, hiccup or apnoea. The duration of apnoea was noted, and the lungs ventilated manually if it was longer than 20 s or if Sp_{O_2} decreased to less than 90%.

Anaesthesia was maintained with halothane and 60% nitrous oxide in oxygen. Heart rate, MAP and Sp_{O_2} were recorded every minute for the first 10 min of anaesthesia. At the end of surgery the halothane concentration was reduced to 0.5% for 3 min. Halothane and nitrous oxide were then discontinued, and the duration of halothane administration was noted.

During the recovery period, all patients received oxygen 4 litre min^{-1} via a Hudson mask. MAP, heart rate and Sp_{O_2} were recorded at 1-min intervals. Recovery scoring was conducted at 1-min intervals by one investigator (N.T.) using a scoring system validated in a previous study (appendix) [3]. Complications including nausea, vomiting, cough, hiccup or laryngeal spasm during the recovery period were recorded. Patients were transferred from the recovery area to the day ward, where any later complications were noted.

STATISTICAL ANALYSIS

Data were analysed using Student's *t* test, the chi-square test and Fisher's exact test, where appropriate. To analyse the recovery profiles, test statistics were constructed using general estimating equations, which were then used to fit a marginal proportional odds model [4].

Results

There were no significant differences ($P < 0.05$) between the two groups in age, sex, preoperative cardiovascular variables or duration of anaesthesia (table 1). For group A (propofol–methohexitone) the

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Table 1 Patient data, preoperative cardiovascular variables and Sp_{O_2} for group A (propofol–methohexitone) and group B (propofol) (mean (range) or number). No significant differences

	Group A ($n = 47$)	Group B ($n = 52$)	P
Age (yr)	46 (20–70)	46 (17–70)	0.94
Sex (M/F)	33/14	33/19	0.48
Heart rate (beat min^{-1})	76 (54–113)	78 (51–111)	0.61
MAP (mm Hg)	106 (76–162)	106 (65–155)	0.88
Sp_{O_2} (%)	97 (92–100)	97 (89–100)	1.00
Duration of anaesthesia (s)	796 (415–3225)	806 (347–2166)	0.91

Table 2 Incidence of complications on induction of anaesthesia in group A (propofol–methohexitone) and group B (propofol). No significant differences

	Group A ($n = 47$)	Group B ($n = 52$)	P
Pain on injection	3	2	0.66
Cough	5	2	0.73
Laryngeal spasm	0	0	
Hiccup	0	2	0.496
Apnoea	25	34	0.22

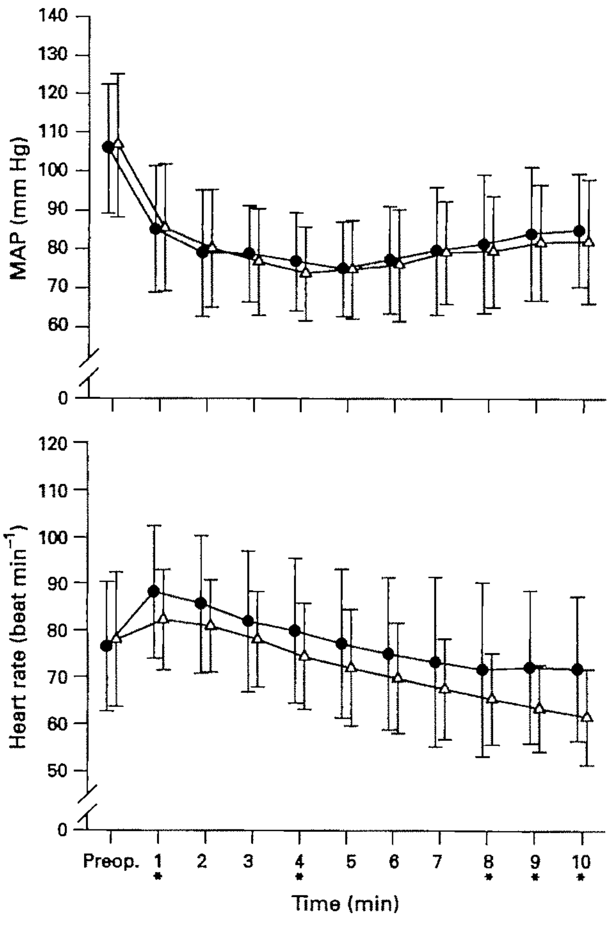

Figure 1 Mean arterial pressure (MAP) and heart rate (mean, SD) before operation (Preop.) and during the first 10 min of anaesthesia for group A (propofol–methohexitone (●)) and group B (propofol (△)). * Significant difference ($P < 0.05$) in heart rate between groups.

Table 3 Incidence of complications on recovery in group A (propofol–methohexitone) and group B (propofol). No significant differences

	Group A ($n = 47$)	Group B ($n = 52$)	P
Cough	7	7	1.00
Laryngeal spasm	0	1	1.00
Hiccup	0	1	1.00

mean volume of induction agent was 17.5 ml (range 12–20 ml) and for group B (propofol) 17 (11–20) ml. One patient in the propofol–methohexitone group exhibited marked spontaneous movement on induction. There were no significant differences in the occurrence of pain on injection, cough, laryngeal spasm, hiccup and apnoea on induction between the groups (table 2).

Heart rate, MAP and Sp_{O_2} were compared between the two groups for each of the first 10 min of anaesthesia. Heart rate was consistently higher in group A, but the difference was significant only at 1, 4, 9 and 10 min (fig. 1). There were no other significant differences in these variables between the two groups at any time during anaesthesia or recovery. One patient in each group exhibited runs of ventricular ectopics during operation, which in both cases were treated successfully with i.v. lignocaine. One patient in the propofol group required atropine 0.3 mg i.v., after 5 min of anaesthesia to treat a bradycardia of 43 beat min^{-1}.

Mean time to full recovery was similar in both groups (group A, 7 (SD 3.7) min, group B, (6.7 (3.1) min; ns). Comparison of the changes with time of the various elements of the recovery scores was made using a marginal proportional odds model. This revealed no difference in the time profiles of recovery between the two groups. There was no significant difference in complication rates during recovery (table 3).

Discussion

In day-case anaesthesia, propofol is the "gold-standard" by which other induction agents are judged. However, its superior recovery profile [2, 5, 6] and relative infrequency of postoperative complications [1, 5, 7] are offset by its tendency to cause apnoea on induction [2, 5] and greater cardiovascular instability than other induction agents [2, 5, 6].

Although specific information on the compatibility and stability of mixtures of propofol and methohexitone is not available, the data sheets on the use of these drugs did not suggest any obvious risk of physical or chemical incompatibility. It is recommended that, because of differences in pH, solutions of methohexitone should not be mixed with acid solutions. As the pH of propofol is 7.5, and that of the propofol—methohexitone mixture 8.9 [personal observation], physical incompatibility would be unlikely. The remarkably similar mean volumes of the induction agents (17.5 ml and 17 ml) provides further circumstantial evidence that no significant pharmacological interaction or change in drug potency took place in the drug mixture. The 1:2

Table 4 Comparison of properties of propofol and propofol–methohexitone in this study with properties of propofol and of methohexitone described in previous studies (all values are given as percentages)

	Propofol (this study)	Propofol–methohexitone (this study)	Propofol (previous studies)	Methohexitone (previous studies)
Pain on injection	4	6	0–48 [1,2,6,9,10,12]	4–56 [2,6,9,10,13]
Cough	8	11	12 [2]	32 [2]
Laryngeal spasm	0	0	—	12 [2]
Hiccup	4	0	0–5 [2,6,9]	24–40 [2,6,9]
Spontaneous movement	0	2	0–10 [2,6,9]	0–24 [2,6,9]
Apnoea	65	53	12–60 [2,5,10]	14–36 [2,10,11]
Postoperative nausea and vomiting	0	0	1.9–20 [2,6,7,9]	20–40 [2,6,11]

dilution of propofol in this study is well within the recommended maximum dilution of 1:5 using solutions such as 5% glucose, and a previous study using mixtures of propofol and alfentanil did not cause any pharmacodynamic or physical instability [8]. For the purposes of this study, in view of the recommendation that dilutions of propofol should be used within 6 h, mixtures made more than 2 h previously were discarded. No visible layering, separation or development of particles occurred at any time in the drug mixtures.

In this study, the behaviour of the propofol–methohexitone mixture was indistinguishable clinically from that of propofol alone during induction, maintenance and recovery. While the propofol–methohexitone group maintained a slightly higher heart rate during the first 10 min of anaesthesia (fig. 1), clinically this was not noticeable or significant. Changes in MAP were similar in both groups (fig. 1), although it might have been anticipated that the drug mixture would have caused less reduction in MAP because of the lesser hypotensive effect of methohexitone [2, 5, 6, 10].

Compared with the results of previous studies (table 4), the propofol–methohexitone mixture compared favourably with methohexitone alone in all aspects except the incidence of apnoea on induction, which was higher with the drug combination, presumably reflecting the addition of propofol. In this study both groups had a lower incidence of pain on injection (because of the addition of lignocaine [12, 13]), and of postoperative nausea and vomiting than described previously.

At present in the UK propofol costs £4.42 for a 200-mg ampoule. Methohexitone costs 41p for a 50-mg dose from a 500-mg ampoule mixed to 0.5% strength with water or saline; 20 ml of a 50:50 propofol–methohexitone mixture would therefore cost £2.62, a cost saving of £1.80 per patient compared with propofol. In a day-case unit treating 5000 patients per annum, this would represent an annual saving of approximately £9000 at current prices. The inconvenience of mixing methohexitone and preparing syringes was found by the authors to be negligible.

Appendix

RECOVERY SCORING SYSTEM

	Score
Consciousness	
Fully awake; eyes open; conversing	4
Lightly asleep; eyes opening intermittently	3
Eyes open on command or in response to name	2
Responding to ear pinching	1
Not responding	0
Airway	
Opening mouth or coughing, or both, on command	3
No voluntary cough, but airway clear without support	2
Airway obstructed on neck flexion but clear without support on extension	1
Airway obstructing without support	0
Activity	
Raising one arm on command	2
Non-purposeful movement	1
Not moving	0

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References

1. Sanderson JH, Blades JF. Multicentre study of propofol in day case surgery. *Anaesthesia* 1988; 43 (Suppl.): 70–73.
2. O'Toole DP, Milligan KR, Howe JP, McCollum JSC, Dundee JW. A comparison of propofol and methohexitone as induction agents for day case isoflurane anaesthesia. *Anaesthesia* 1987; 42: 373–376.
3. Robertson GS, MacGregor DM, Jones CJ. Evaluation of doxapram for arousal from general anaesthesia in outpatients. *British Journal of Anaesthesia* 1977; 49: 133–139.
4. Kenward MG, Lesaffre E, Molenberghs G. An application of maximum likelihood and generalised estimating equations to the analysis of ordinal data from a longitudinal study with cases missing at random. *Biometrics* 1994, 50: 945–953.

5. Mackenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *British Journal of Anaesthesia* 1985; **57**: 725–731.
6. Raeder JC, Misvaer G. Comparison of propofol induction with thiopentone or methohexitone in short outpatient general anaesthesia. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 607–613.
7. McLeskey CH, Walawander CA, Nahrwold ML, Roizen MF. Adverse events in a multicentre phase IV study of propofol: evaluation by anesthesiologists and postanesthesia care unit nurses. *Anesthesia and Analgesia* 1993; 77 (4 Suppl.): S3–9.
8. Taylor IN, Kenny GN, Glen JB. Pharmacodynamic stability of a mixture of propofol and alfentanil. *British Journal of Anaesthesia* 1992; **69**: 168–171.
9. Heath PJ, Kennedy DJ, Ogg TW, Dunling C, Gilks WR. Which intravenous induction agent for day surgery? A comparison of propofol, thiopentone, methohexitone and etomidate. *Anaesthesia* 1988; **43**: 365–368.
10. Wells JKG. Comparison of ICI 35868 etomidate and methohexitone for day-case anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 732–735.
11. Goroszeniuk T, Whitwam JG. Morgan M. Use of methohexitone, fentanyl and nitrous oxide for short surgical procedures. *Anaesthesia* 1977; **32**: 209–211.
12. Helbo-Hansen S, Westergaard V, Krogh BL, Svendsen HP. The reduction of pain on injection of propofol: the effect of addition of lignocaine. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 502–504.
13. Simpson KH, Halsall PJ, Sides CA, Keeler JF. Pain on injection of methohexitone. The use of lignocaine to modify pain on injection of methohexitone during anaesthesia for electroconvulsive therapy. *Anaesthesia* 1989; **44**: 688–689.

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ASA classification and perioperative variables as predictors of postoperative outcome

U. WOLTERS, T. WOLF, H. STÜTZER AND T. SCHRÖDER

Summary

In a prospective study of 6301 surgical patients in a university hospital, we examined the strength of association between ASA physical status classification and perioperative risk factors, and postoperative outcome, using both univariate analysis and calculation of the odds ratio of the risk of developing a postoperative complication by means of a logistic regression model. Univariate analysis showed a significant correlation ($P < 0.05$) between ASA class and perioperative variables (intraoperative blood loss, duration of postoperative ventilation and duration of intensive care stay), postoperative complications and mortality rate. Univariate analysis of individual preoperative risk factors demonstrated their importance in the development of postoperative complications in the related organ systems. Estimating the increased risk odds ratio for single variables, we found that the risk of complication was influenced mainly by ASA class IV (risk odds ratio = 4.2) and ASA class III (risk odds ratio = 2.2). We conclude that ASA physical status classification was a predictor of postoperative outcome. (*Br. J. Anaesth.* 1996; **77**; 217–222).

Key words

Complications, ASA classification. Assessment, ASA classification. Complications, postoperative. Recovery, postoperative. Organisations, American Society of Anesthesiologists.

The American Society of Anesthesiologists' (ASA) classification of physical status was introduced in 1941 by Saklad [1] in an attempt to provide a basis for comparison of statistical data in anaesthesia. The classification was revised in 1963 [2] with the number of classes being reduced from seven to five. Several retrospective studies have demonstrated a correlation between ASA classification and perioperative mortality [3–8], and have suggested its usefulness as a predictor of patient outcome. Prospective studies correlating ASA classification with both perioperative mortality and morbidity have suffered either from small patient numbers [4] or from focusing only on anaesthetic complications [9, 10].

The aim of this prospective study was to evaluate the prognostic value of ASA classification with regard to perioperative variables such as blood loss, duration of intensive care stay, postoperative complications and mortality. In addition, we investigated the relationship between the presence of specific preoperative disease states (arterial hypertension, previous myocardial infarction, smoking and severe bronchopulmonary disease) and the development of major postoperative complications (cardiac and pulmonary), and the need for postoperative ventilation. Further, we used logistic regression analysis to provide an estimate of the risk odds ratio implied by specific perioperative variables, together with an estimate of the risk odds ratio when more than one perioperative variable was considered.

Patients and methods

All patients operated on in the Department of General and Vascular Surgery, University of Cologne, between May 1, 1989 and April 30, 1993, were included prospectively in the study. All patients were assessed before operation by an anaesthetist, wherever possible. Assignation of the 1963 ASA classification (table 1) was performed by two anaesthetists, of which at least one was a consultant. The standard anaesthetic record was used. Specific data retrieved from the anaesthetic record were: ASA classification; emergency or elective operation; the presence of specific preoperative disease states (anaemia, defined as haemoglobin concentration < 100 g litre^{-1} or arterial hypertension systolic pressure > 160 mm Hg); previous myocardial infarction; previous stroke; smoking (positive if > 20 cigarettes per week); severe bronchopulmonary disease (vital capacity or forced expiratory volume in 1 s $< 40\,\%$ of predicted); diabetes mellitus (all types requiring medication); acute or chronic renal failure (serum creatinine > 1.5 mg dl^{-1}); and major gastrointestinal diseases (e.g. ulcerative colitis, gastric or duodenal ulcer). Type of anaesthesia, operation performed, operating time (time from skin incision to wound closure) and intraoperative blood loss, as estimated by the anaesthetist, were also recorded.

Operations were classified according to the Hoehn system [11], as used frequently in Germany, into

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Table 1 American Society of Anesthesiologists' (ASA) physical status classification

Class	Description
I	Healthy patient
II	Mild systemic disease—no functional limitation
III	Severe systemic disease—definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 h with or without operation

minor (e.g. repair of soft tissue wounds, perineal surgery), moderate (colostomy formation, cholecystectomy, herniotomy) or major (bowel resection, thoracic surgery, abdominal and peripheral vascular interventions). Preoperative investigations in all patients undergoing moderate and major operations included serum electrolyte (Na^+, K^+, Cl^-), creatinine and glucose concentrations, blood count (haemoglobin, packed cell volume, platelet count, leucocyte count), coagulation screen (prothrombin time, partial thromboplastin time), chest x-ray and an ECG. Also, all patients received cephazolin (Elzogram 2 g) i.v. and single-dose low molecular weight heparin (Dalteparin sodium 7500 i.v.) s.c. after induction.

Postoperative data were obtained by surgical interns and final year medical students. Attention was focused on pulmonary complications such as bronchopulmonary infection, as diagnosed by positive sputum culture or positive chest x-ray, or both, atelectasis or pleural effusion, as seen on the chest x-ray. Significant arrhythmias such as new atrial fibrillation or acute myocardial infarction confirmed by ECG changes and increases in CPK-MB enzymes were recorded as cardiac complications. Wound inflammation or a purulent wound discharge was recorded as a wound infection, and clinically apparent anastomotic leakage was also noted. Culture-positive urinary tract infections were also recorded.

The data were summarized into two groups. First, to allow comparison between ASA classification and perioperative variables, we recorded duration of operation, intraoperative blood loss, duration of postoperative ventilation, stay in intensive care, postoperative hospital stay, and rates of pulmonary complications, cardiac complications, wound infection, anastomotic leakage, urinary tract infection and in-hospital mortality (expressed as means). The second grouping allowed a univariate analysis of the relationship between the most prevalent preoperative disease states and the incident of major postoperative events. Finally, logistic regression was applied to the data to estimate the risk odds ratio of single and combined perioperative variables.

STATISTICAL METHODS

The Student's *t* test was used to quantify the difference in the means of independent perioperative variables between ASA classifications. Differences in the rates of complications between ASA classifications were assessed by Fisher's exact test. The significance of the impact of preoperative disease states on the development of a specific postoperative complication was also assessed by Fisher's exact test. The logistic regression model is explained in the appendix.

Results

A total of 6301 patients were operated on in the sample period and patient data are summarized in table 2. More than 75 % of patients were classified as ASA II or III (table 3). As only 15 patients (0.2 %) were classified as ASA V and as 14 of these patients died in hospital, they were excluded from statistical analysis on morbidity.

There were a total of 9136 pre-existing disease states in 6301 patients (table 4). The major preoperative disease states identified were arterial hypertension, smoking, severe bronchopulmonary disease and major gastrointestinal disease, each with an incidence of more than 20 %. The type of operation according to Hoehn system was 1004 (16 %) minor, 1695 (27 %) moderate and 3602 (57 %) major. All ASA V patients underwent major operations. The specific sites of operation are summarized in table 5. As an indication of the type of operation performed, the 1077 operations listed as "colon and rectum" included mainly partial and total colectomy, and the 1495 operations listed as "vascular" included aortic procedures and carotid surgery.

Table 2 Patient data (mean (SD) [range] or number (%))

Total number of patients	6301
Males	3699 (59 %)
Females	2602 (41 %)
Emergency operations	1279 (20 %)
Malignant disease identified	1631 (26 %)
Age (yr)	52 [0–98]
Type of anaesthesia	
General	97.5 %
Regional	1.4 %
Combined	1.1 %
Operating time (min)	107 (48.2) [5–830]
Postoperative stay (days)	12 (2.8) [1–132]
Hospital stay (days)	16.5 (3.4) [1–179]

Table 3 ASA classification of all patients

	n	%
ASA I	1133	18
ASA II	2685	42.6
ASA III	2181	34.6
ASA IV	290	4.6
ASA V	15	0.2

Table 4 Incidence of specific preoperative disease status

	n	%
Anaemia	501	8
Arterial hypertension	1817	28
Previous myocardial infarction	272	4
Previous stroke	460	7
Positive smoking history	1823	28
Severe bronchopulmonary disease	1353	21
Diabetes mellitus	685	11
Acute or chronic renal failure	685	11
Major gastrointestinal disease	1540	24

Table 5 Sites of surgery for the 6301 patients

Site of surgery	*n*	%
Thyroid and parathyroid	421	6.7
Oesophagus	283	4.5
Gastric	232	3.7
Small bowel	172	2.7
Colon rectum	1077	16.9
Biliary tract	358	5.7
Liver	137	2.2
Pancreas	66	1
Spleen	74	1.7
Adrenal gland, kidney	69	1
Hernia	600	9.4
Kidney transplant	235	3.7
Other abdominal surgery	314	5
Breast surgery	23	0.4
Extra-abdominal lymph nodes	106	1.7
Other neck surgery	32	0.5
Soft tissue tumours	210	3.3
Vascular	1495	23.6
Thoracic	397	6.3

For perioperative variables in relation to ASA (table 6), we found an increase in duration of operation between ASA I and ASA II–IV combined ($P < 0.05$) and between ASA II and III ($P < 0.05$). Intraoperative blood loss was 5–20-fold greater in ASA IV than in ASA I–III groups ($P < 0.05$). We found a 2–6-fold increase in the duration of postoperative ventilation between individual groups ($P < 0.05$). Postoperative intensive care and total hospital stay of ASA II–IV patients were 1–5 and 7–11 days longer, respectively, than in ASA I ($P < 0.05$). We found a 2–3-fold incidence of postoperative bronchopulmonary complications in a stepwise manner through each ASA class ($P < 0.05$). A threefold increase in cardiac complications was found between individual classes I–IV ($P < 0.05$). The incidence of postoperative wound and urinary tract infections was 2–3 times greater in ASA classes II–IV than in ASA class I (I *vs* II–IV, $P < 0.05$). Postoperative anastomotic leakages were independent of ASA class. We found a significant 5–7-fold stepwise increase in hospital mortality per ASA class.

The relationship between specific preoperative disease states and individual postoperative complications is shown in table 7. Arterial hypertension and previous myocardial infarction implied a 50% increase in the rate of developing a cardiac complication, and previous myocardial infarction implied longer postoperative ventilation. Severe bronchopulmonary disease implied a significant increase in the chance of developing a cardiac or pulmonary complication and increased duration of postoperative ventilation. We did not find that smoking was a significant factor in the development of the four major postoperative complications.

The logistic regression analysis data are summarized in table 8. The highest risk odds ratios for developing a postoperative complication were associated with worsening ASA classification and a "major" *vs* a "moderate" or "minor" operation, as per the Hoehn classification. Particularly, assignation of ASA IV implied a risk odds ratio of 4.26, that is a 4.26 times higher risk of developing a postoperative complication than for ASA I. As-

Table 6 Preoperative variables in relation to ASA. * Chi-square analysis by Fisher's exact test; † Student's *t* test

	ASA I	ASA II	ASA III	ASA IV	*P*
Operation duration (min)	75	108	124	116	< 0.05†
Intraoperative blood loss (ml)	78	105	293	1548	< 0.05†
Postoperative ventilation (h)	1.1	4.2	7.7	46.5	< 0.05†
Intensive care stay (days)	0.2	0.8	1.9	5.4	< 0.05†
Postoperative stay (days)	9.3	16.4	20.8	17.6	< 0.05†
Bronchopulmonary infection (%)	0.5	2.2	5.2	12.1	< 0.05*
Other pulmonary complications (%)	0.6	2.1	4.3	9.9	< 0.05*
Cardiac complications (%)	0.1	1.5	5.5	18	< 0.05*
Wound infection (%)	1.8	3.8	6.3	10.6	< 0.05*
Anastomotic leakage (%)	0.6	1.3	1.5	1.6	0.14456*
Urinary infection (%)	2.1	4.6	6.1	5	< 0.05*
Mortality (%)	0.1	0.7	3.5	18.3	< 0.05*

Table 7 Univariate analysis of preoperative disease status in relation to postoperative complications. *$P < 0.05$

	Postoperative ventilation (h) (mean (SD))	Cardiac complications (%)	Pulmonary complications (%)	Pneumonia (%)	Mortality (%)
Arterial hypertension (%)					
Yes	7.4 (37.3)	4.8	3.4	4.0	2.9
No	6.5 (29.8)	2.7*	2.8	3.0	1.5
Previous myocardial infarction (%)					
Yes	13.7 (52.2)	7.2	4.5	4.2	4.2
No	6.4 (34.3)*	3.1*	2.9	3.2	1.8
Severe bronchopulmonary disease (%)					
Yes	10.6 (45.5)	5.9	5.5	5.8	3.8
No	5.7 (32.0)*	2.6*	2.3*	2.6*	1.4*
Smoker (%)					
Yes	6.3 (30.8)	3.3	3.3	4.9	1.9
No	6.9 (37.0)	3.3	2.8	2.6*	1.9

Table 8 Risk factors for postoperative complications. [a] β, estimated regression coefficient, [b] standard error of β, [c] P value for Wald's test, [d] odds ratio related to reference class adjusted for all other independent variables in the model, [e] 95% confidence intervals for the odds ratio, [f] reference class is set to ASA I: ASA (1) = indicator for class ASA II; ASA (2) = indicator for class ASA III; ASA (3) = indicator for class ASA IV, [g] "Major" operations compared with "moderate" or "minor" operations, as per the Höhn classification

Independent variables (poorer class or "yes" coded 1)	Logistic regression variables and statistics				
	β(a)	SE(b)	P(c)	Risk ratio(d)	95% CI(e)
ASA(f)			< 0.00005		
ASA (1)	0.45	0.1319	0.0007	1.5668	1.21; 2.03
ASA (2)	0.81	0.1400	< 0.00005	2.2457	1.71; 2.96
ASA (3)	1.45	0.1855	< 0.00005	4.2600	2.96; 6.13
Class of operation(f,g)	0.63	0.0783	< 0.00005	1.8604	1.61; 2.19
Emergency	0.21	0.0440	< 0.00005	1.2366	1.13; 1.34
Renal insufficiency	0.33	0.1010	0.0008	1.3976	1.14; 1.70
Anaemia	0.21	0.0921	0.0259	1.2279	1.03; 1.48
Bronchopulm. disease	0.26	0.0763	0.0009	1.2911	1.12; 1.51
History of smoking	0.15	0.0718	0.0346	1.1638	1.01; 1.34
Age (yr)	0.01	0.0022	< 0.00005	1.0105	1.0006; 1.014
Op. duration (min)	< 0.0001	< 0.0001	< 0.00005	1.0001	1.0001; 1.000
Constant	−3.5622	0.1475	< 0.00005		

signation of ASA II and III implied risk odds ratios of 1.57 and 2.25, respectively. A moderate increase in the risk odds ratio was also seen in patients with renal disease, anaemia, bronchopulmonary disease and in those undergoing emergency operations.

Discussion

The ASA classification has established itself as the most widely used patient risk assessment scheme in anaesthesia, despite being developed in 1941 by Saklad [1] for the purpose of statistical data management. The 1963 revision eliminated the emergency classes of the original version and an emergency operation is noted by placing an "E" after the remaining five classes. No other preoperative risk assessment scheme developed has achieved the same widespread use. Other internationally known patient scoring systems outside the field of anaesthesia include APACHE II [12], used widely in intensive care, but the need for a 24-h sampling period of 12 routine physiological measurements, age and previous health status underlies the unsuitability of this system for anaesthesia. The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) was presented by Copeland, Jones and Walters in 1991 [13] and is based on a point score derived from 12 physiological and six operative severity score factors. The authors' intention was to develop a score to aid surgical audit and thus their method does not give the full score and the numerical estimate of the risk of mortality and morbidity until the outcome is known. In contrast, the ASA classification represents a simple estimation of physiological status without the need for clinical resources and can be applied to every patient before operation.

A major drawback of the ASA system is assessment of a patient's "correct" ASA classification by different anaesthetists and this was shown clearly by Owens, Felt and Spitznagel [14]. In their study, 304 anaesthetists were requested to classify 10 hypothetical patients and the mean numbers of patients rated identically by the authors and the responders was 5.9 (mode 6). To minimize this variability in our study, assignation of ASA class was performed by two experienced anaesthetists adhering strictly to the 1963 criteria (table 1). It is important to remember that these criteria do not take into account age and the complexity of operation, and there is no differentiation between a systemic disease that leads to operation and one that is an incidental chronic finding.

Few studies have examined the relationship between ASA physical status and perioperative morbidity. Cohen, Duncan and Tate [15] studied anaesthetic complications in the intraoperative period and in the recovery room (e.g. cardiac arrest, hypotension, aspiration). Tiret and Hatton [10] reported similar major complications during or within 24 h of anaesthesia. Both studies found significant correlations between these anaesthetic complications and patient ASA classification.

Our data identified several specific intra- and postoperative variables correlated significantly with ASA classification. Intraoperative blood loss, duration of postoperative ventilation, duration of intensive care stay, rates of pulmonary and cardiac complications, and in-hospital mortality showed significant increases as patient ASA defined status advanced from I to IV, with a 20–180-fold difference between ASA I and IV, and an average 2.8- and 3.7-fold difference in these variables between ASA II and III, and ASA III and IV, respectively. The high incidence of perioperative morbidity in ASA classes III and IV, especially pulmonary and cardiac complications (4–18%), supports the concept of directing therapy, particularly ventilatory support and other intensive care resources, towards these patients.

The correlation between ASA classification and postoperative mortality has been shown in several previous studies [3, 5–8] and was confirmed by our data. The published absolute mortality rates of the individual classes showed considerable variation, with 0–0.3% for ASA I, 0.3–1.4% for ASA II, 1.8–5–4% for ASA III, 7.8–25.9% for ASA IV and 9.4–57.8% for ASA V. This variation may be explained by differences in assessment of the patient's ASA physical status, patient population, sample size, operations performed and duration of postoperative monitoring. The latter is particularly important, as some of the older studies included only deaths occurring within the first 48 h [6] or within the first 7 days [5] after operation, while none covered the whole hospital stay. Thus these studies missed almost 50 % of postoperative in-hospital deaths occurring after the seventh postoperative day [3]. Often these limits are placed to assess the possible role of anaesthesia in postoperative mortality. In contrast, our data, with mortality rates of 0.1 % for ASA I, 0.7 % for ASA II, 3.5 % for ASA III, 18.3 % for ASA IV and 93.3 % for ASA V, were based on all deaths in hospital after surgical intervention, as we wished to quantify the total in-hospital risk.

Univariate analysis of four major preoperative disease states against individual postoperative complications (table 7) demonstrated their role in the development of complications in the related organ systems. This information is of little impact as patients usually have more have one significant pre-existing disease and it cannot be used to quantify the relative risk. Therefore, our study attempted to quantify the importance of specific risk factors in the evaluation of surgical outcome using multiple risk analysis as the appropriate statistical method. This was done as a means of eliminating the interference of these variables, as in previous studies [9, 12, 13]. The risk odds ratio (ROR), reflecting the relative increase in the complication risk of a single variable, was calculated by multivariate analysis and stepwise regression. The highest risk odds ratio of 4.26 was calculated for ASA IV, followed by ASA III (ROR 2.25), class of operation (ROR 1.86), ASA II (ROR 1.57) and emergency operation (ROR 1.24).

All other variables were of minor significance. Again, this highlights the value of the ASA classification system for the prediction of postoperative complications. A similar conclusion was reached by Pedersen and colleagues [4] who evaluated the possible relationship of 35 preoperative variables to only one event: the need for postoperative mechanical ventilation in a 3-month screening study. The best predictor of all variables was an ASA classification of greater than III. To assess the role of the complexity of an operation as an independent risk factor, previous studies divided the interventions into two groups (minor/major) [9], or into four groups (minor/moderate/major/major+) [13]. Applying the Hoehn classification [11], we differentiated three classes and found no significant difference between minor and moderate interventions, whereas major operations implied an almost doubled risk of complications.

The relative risk of 1.24 for patients undergoing emergency operations developing a postoperative complication was lower than risk odds ratios reported previously. Tiret and Hatton reported an ROR of 2.0 for intraoperative complications [10], Pedersen and colleagues 2.1 for the risk of postoperative ventilation [4] and Cohen, Duncan and Tate 4.4 for the risk of dying within 7 days [15] after an emergency operation.

Forrest and colleagues [16] showed that ASA classes III and IV were major predictors for severe cardiorespiratory outcome in a study which included only patients for elective surgery.

To extend the use of the multivariate risk analysis concept, the impact of more than one variable can be assessed using the formulae in the appendix, together with estimated regression coefficients derived from the logistic regression analysis of our data. This attempted quantification of "total" relative risk is of great value as it could lead to improvement in patient therapy.

Appendix

The goal of logistic regression analysis is to describe the relationship between a prospectively observed dichotomous outcome (the occurrence of a postoperative complication or not—the dependent variable) and a set of independent indicator variables (perioperative variables in our model) by modelling the probability "P" of the outcome by an expression of the form:

$$P = \frac{1}{1+e^{-g(X)}} \tag{1}$$

where $g(X) = \beta_0 + \beta_1 X_1 + \ldots + \beta_n X_n$, β_0 = model constant, $\beta_{1\ldots n}$ = regression coefficients (estimated by maximum likelihood methods) and $X_{1\ldots n}$ = independent predictor variables coding perioperative clinical risk factors.

In our model there are three types of predictor variables: (i) those coding the dichotomous state yes/no (i.e. presence or not) of known clinical variables before operation, such as broncho-pulmonary disease or an emergency operation; these are usually coded "1" if a clinically poorer status is present and otherwise "0"; (ii) those variables coding values of continuous variables such as duration of operation; (iii) those categorical or ordinal items, such as ASA classification, where "dummy" using $k-1$ indicator variables for k categories of the item is set up. To simplify our model, the reference category for ASA status was set to ASA 1 and indicator variables for ASA II, III and IV termed ASA (1), ASA (2) and ASA (3), respectively (table A1).

To calculate the risk odds ratio (ROR) for an outcome we use:

$$\frac{P}{1-P} = e^{g(X-x)} \tag{2}$$

which by substitution becomes ROR =

$$e^{\beta} \quad \text{or} \quad e^{c\times\beta} \text{ respectively} \tag{3}$$

and may be estimated for each risk pattern.

An estimator for the multiplicative change in the ROR when switching an indicator variable to poorer status, leaving the values of all other independent variables fixed, is given by the expression:

$$e^{\beta} \tag{4}$$

An estimator for 100 $(1-\alpha)$ % confidence interval for the ROR is given by:

$$e^{\beta \pm 1.96\,\mathrm{SE}(\beta)} \tag{5}$$

where $\mathrm{SE}(\beta)$ = standard error of the regression coefficient β belonging to the variable studied for the change in ROR.

To obtain an estimate of the ROR of multiple variables we used equation (4). For example, using table 8, the ROR for a population with the risk pattern (a):

Table A1 Indicator variables for ASA categories

ASA status	Indicator variables		
	ASA (1)	ASA (2)	ASA (3)
I	0	0	0
II	1	0	0
III	0	1	0
IV	0	0	1

(a) ASA = II

Emergency operation = yes
Bronchopulmonary disease = yes
Smoker = yes

relative to a population with risk pattern (b):

(b) ASA = I

Emergency operation = no
Bronchopulmonary disease = no
Smoker = no

and with equal values for all other risk variables, is estimated through:

$$e^{(0.45+0.21+0.26+0.15)} = 2.9 \approx 3 \qquad (6)$$

In terms of relative risk this indicates that a postoperative complication may occur approximately three times as often among patients with risk pattern (a) than among patients with risk pattern (b), assuming all other clinical risk factors are identical.

References

1. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* 1941; **2**: 281–284.
2. American Society of Anesthesiologists. New classification of physical status. *Anesthesiology* 1963; **24**: 111.
3. Farrow SC, Fowkes FG, Lunn JN, Robertson IB, Samuel P. Epidemiology in anaesthesia II: Factors affecting mortality in hospital. *British Journal of Anaesthesia* 1982; **54**: 811–817.
4. Pedersen T, Eliasen K, Ravnborg M, Viby-Mogensen J, Qvist J, Johansen SH, Henriksen E. Risk factors, complications and outcome in anaesthesia. A pilot study. *European Journal of Anaesthesia* 1986; **3**: 225–239.
5. Marx GH, Matteo CV, Orkin LR. Computer analysis of post anesthetic deaths. *Anesthesiology* 1973; **39**: 54–58.
6. Vacanti CJ, Van Houten RJ, Hill RC. A statistical analysis of the relationship of physical status to postoperative mortality in 68388 cases. *Anesthesia and Analgesia* 1970; **49**: 564–566.
7. Menke H, John KD, Klein A, Lorenz W, Junginger Th. Präoperative Risikoeinschätzung mit der ASA-Klassifikation. Eine prospektive Untersuchung zu Morbidität und Letalität in verschiedenen ASA-Klassen bei 2937 Patienten mit allgemeinchirurgischen Operationen. *Chirurg* 1992; **63**: 1029–1034.
8. Feigal DW, Blaisdell FW. The estimation of surgical risk. *Medical Clinics of North America* 1979; **63**: 1131–1143.
9. Cohen MM, Duncan PG. Physical status score and trends in anesthetic complications. *Journal of Clinical Epidemiology* 1988; **41**: 83–90.
10. Tiret L, Hatton F. Prediction of outcome of anaesthesia in patients over 40 years: a multifactorial risk index. *Statistics in Medicine* 1988; **7**: 947–954.
11. Höhn HG. Operationskatalog für Betriebsvergleiche. *KU* 1972; **2**: 112–131.
12. Knaus WA, Draper EA, Wagner DP. Apache II: a severity of disease classification system *Critical Care Medicine* 1985; **13**: 818–829.
13. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *British Journal of Surgery* 1991; **78**: 356–360.
14. Owens WB, Felts JA, Spitznagel EL. ASA physical status classifications: A study of consistency of ratings. *Anesthesiology* 1978; **49**: 239–243.
15. Cohen MM, Duncan PG, Tate RB. Does anaesthesia contribute to operative mortality? *Journal of the American Medical Association* 1988; **260**: 2859–2863.
16. Forrest JB, Rehder K, Cahalan MK, Goldsmith CH. Multicenter study of general anesthesia. III. Predictors of severe perioperative adverse outcomes. *Anesthesiology* 1992; **76**: 3–15.

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Time course of increased haemodilution in hypotension induced by extradural anaesthesia

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Summary

Volume loading with crystalloid solution results in more pronounced haemodilution in patients who develop arterial hypotension during induction of extradural anaesthesia than in those who remain normotensive. The aim of this study was to describe the time course of this increase in haemodilution. Heart rate, systolic arterial pressure and blood haemoglobin concentration were measured every 3 min during the onset of extradural anaesthesia in 22 elderly men undergoing short urological operations. Fluid therapy consisted of 15 ml/kg body weight of Ringer's acetate solution. Patients with a decrease in systolic pressure of > 25% retained 50% (SD 12%) of the infused fluid in the circulation, while the others retained 36 (8%) ($P < 0.002$). In both groups, arterial hypotension was followed by increased haemodilution after a delay of as much as 15 min. This suggests that, despite volume loading, there is relative hypovolaemia throughout the development of hypotension. (*Br. J. Anaesth.* 1996; **77**; 223–226).

Key words

Anaesthetic techniques, extradural. Arterial pressure, hypotension. Blood, volume. Fluids, i.v. Blood haemodilution.

Haemodilution is frequently induced by volume loading with a crystalloid solution before lumbar extradural anaesthesia or spinal anaesthesia is induced. The aim is to prevent a decrease in arterial pressure (AP) by increasing blood volume. However, the body's handling of crystalloid solutions is altered during the onset of these neural blocks. Elderly men who maintain a normal AP retain about 30 % of the solution given for volume loading in the circulation, while this fraction is twice as large in those who show a decrease in AP [1–3]. Thus blood volume increases in proportion to hypotension. Marked haemodilution has also been described in parturients who develop hypotension during onset of these blocks before Caesarean section [4].

The aim of this study was to see how fast this increased haemodilution develops.

Patients and methods

We studied 22 male patients, ASA I–II, mean age 71 (range 38–85) yr, during induction of extradural anaesthesia before short urological operations. Approval of the Ethics Committee was obtained and each patient gave informed consent.

Premedication consisted of oral oxazepam 25 mg orally. Cannulae were inserted into the antecubital veins of both arms. A fluid load of 15 mg/kg body weight of an isotonic glucose-free crystalloid solution (Ringer's acetate) was infused into one of these veins at a constant rate over 50 min with the aid of two infusion pumps (IVAC 560, San Diego, CA, USA). After 20 min, extradural anaesthesia was induced with 2 % mepivacaine and adrenaline 1:200000 (Carbocain–adrenalin, Astra, Södertälje, Sweden). A test dose of 3 ml of the anaesthetic solution was administered into the extradural space via an indwelling catheter when 20 min had elapsed since the onset of volume loading. The main dose was 9–16 ml, depending on body weight, and was given 3 min later.

A blood sample for measurement of blood haemoglobin concentration (Hb) with a Coulter Counter S plus (Counter Electronics, Hialeah, FL, USA; coefficient of variation of 2 %) was obtained on 13 occasions, before any fluid was given, at 10 min and just before the test dose was given at 20 min into volume loading. Thereafter, Hb was measured every 3 min up to 50 min into the study, at which time the fluid had been infused and adequate surgical analgesia had been achieved, as determined by loss of pinprick sensation.

On the same occasions, one of the authors (D.D.) measured systolic AP using a mercury sphygmomanometer. Hypotension was defined as a decrease in systolic AP of > 25 %. Patients who did not fulfil this criterion were considered normotensive. A vasopressor was available for those who developed bradycardia or nausea, but this did not occur.

The amount of fluid infused that remained in the circulation was calculated from the following equation [1–3]:

$$\text{Fluid retained (\%)} = (V_0(\text{Hb}_0/\text{Hb}_n) - V_0)/\text{volume infused}$$

where Hb_0/Hb_n = haemodilution and V_0 = blood volume before treatment, as estimated from the height and weight of the patient [5].

The results are expressed as mean (SD). The methods of statistical evaluation were simple and multiple linear regression analysis, one-way ANOVA and the paired *t* test were used. $P < 0.05$ was considered statistically significant.

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Results

Ten patients developed hypotension during the onset of extradural anaesthesia. There were no significant differences between these patients and normotensive patients in age, systolic AP or the amount of anaesthetic solution given (table 1). However, the extent of analgesia was higher in hypotensive patients, and they retained a larger fraction of the infused fluid in the circulation than normotensive patients.

Table 1 Patient data, systolic arterial pressure (SAP) and amount of fluid infused that was retained in the blood of 22 elderly men in whom lumbar extradural anaesthesia was induced (mean (SD or range)). * SAP decreased to > 25% during the onset of block

	Normotensive	Hypotensive*	ANOVA
n	12	10	
Age (yr)	72 (52–82)	69 (38–85)	
Weight (kg)	80 (13)	77 (13)	
Amount of anaesthetic (ml)	16 (2)	14 (3)	
Extent of analgesia (Th)	7.1 (2.8)	4.3 (1.7)	$P < 0.01$
SAP (mm Hg)			
0 min	138 (25)	155 (24)	
50 min	120 (21)	98 (26)	$P < 0.02$
Amount of fluid retained (%)			
0–50 min	36 (8)	50 (12)	$P < 0.002$

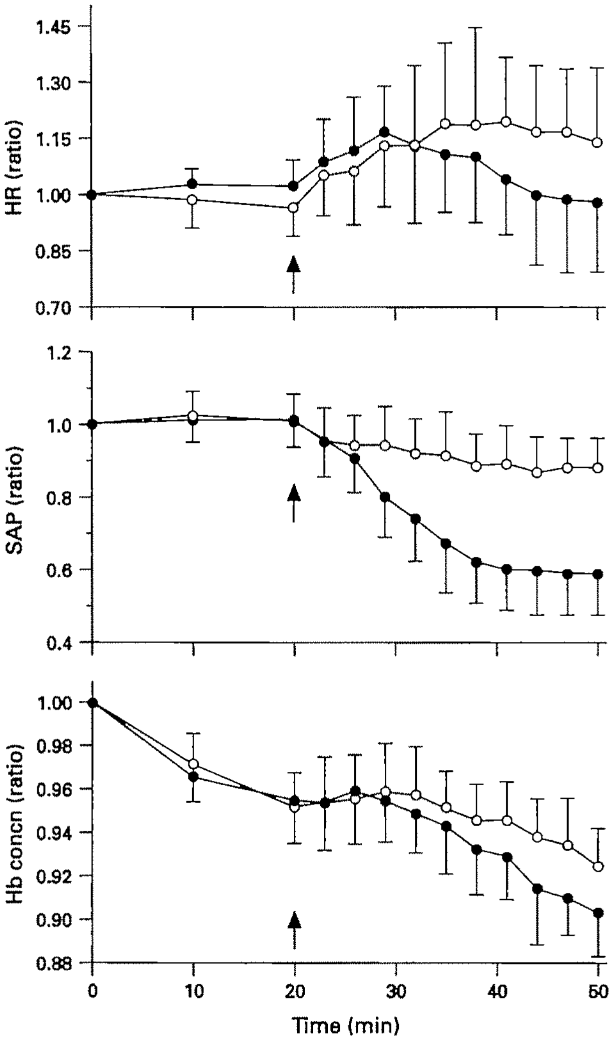

Figure 1 Relative changes in heart rate (HR), systolic arterial pressure (SAP) and haemoglobin (Hb) concentration during volume loading with Ringer's acetate solution and induction of extradural anaesthesia (arrows) in 22 elderly men (mean, SD). Ten patients showed a total decrease in SAP of > 25% (●) while 12 showed a less pronounced decrease (○).

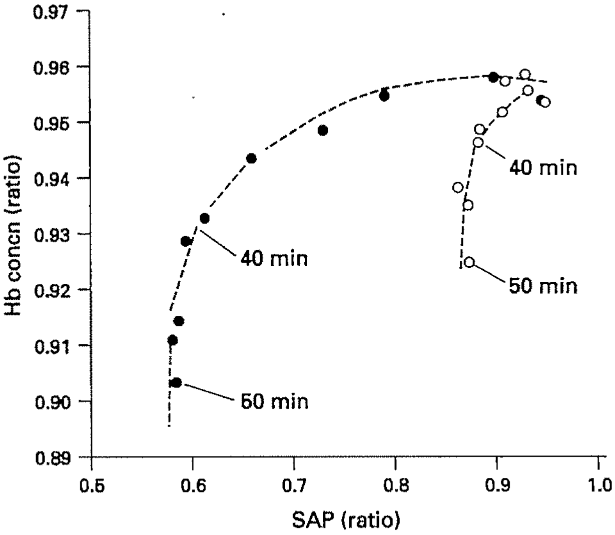

Figure 2 Relative change in systolic arterial pressure (SAP) *vs* haemoglobin (Hb) concentration after the local anaesthetic solution had been injected into the extradural space. The distance between each point on the curves represents a period of 3 min. Data are mean ($n = 22$) and are divided into hypotensive (●) and normotensive (○) patients.

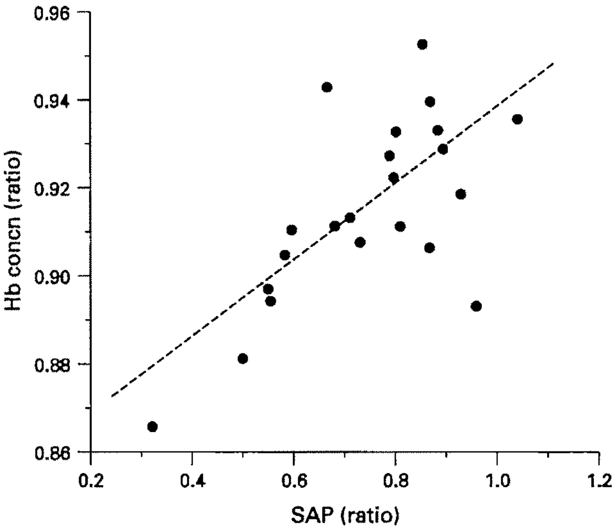

Figure 3 The decrease in systolic arterial pressure (SAP) *vs* haemoglobin (Hb) concentration from before volume loading with Ringer's acetate solution to after extradural anaesthesia had been induced 50 min later. Each point represents one patient ($r = 0.66$, $P < 0.001$).

Heart rate increased significantly during the onset of block in the normotensive patients (paired t test) but remained unchanged in those who showed a decrease in AP (fig. 1, top). The time courses of the changes in systolic AP and haemodilution were the same, irrespective of the magnitude of the hypotensive reaction (fig. 1, middle and bottom). A plot of SAP *vs* haemodilution over time highlights the fact that the time courses in both the hypotensive and normotensive patients consisted of two distinctly different phases, each with a duration of approximately 15 min (fig. 2). The first phase was characterized by a decrease in AP and the second by haemodilution.

The end result (at 50 min) showed a significant linear relationship between the reductions in AP and Hb in all patients (fig. 3). Multiple regression analysis confirmed that no other factor, including haemodilution during the initial 20 min of volume loading ($P = 0.12$) and baseline AP ($P = 0.39$), correlated with haemodilution during the onset of the block. There was no correlation between the initial haemodilution and hypotension.

Discussion

Inadequate circulating blood volume is still believed to be the main mechanism responsible for hypotension during the onset of extradural anaesthesia. [6]. Blood is pooled in the capacitance vessels of the legs at the expense of cardiac filling [7]. The increased haemodilution in hypotensive patients probably indicates an altered relationship in compliance for volume expansion between the intravascular fluid compartment and the interstitial fluid, to the advantage of the dilated intravascular fluid compartment. As vasodilatation is more widespread in patients with high-level extradural block, they also have more haemodilution.

This study showed that the fluid shift typical of vasodilatation develops more slowly than expected. To maintain venous return, each incremental increase in vascular capacitance would have to be followed by prompt and proportional haemodilution, but this apparently does not occur. Increased haemodilution is a dynamic process that can be regarded as two successive phases of change in the relationship between AP and Hb concentration. The most rapid reductions in AP and Hb differed by as much as 15 min. The delay before hypotension was followed by haemodilution, suggesting that relative hypovolaemia persisted throughout the onset of extradural anaesthesia. Therefore, our findings might be relevant to the fact that volume loading is ineffective in preventing hypotension [8–10].

The delay before haemodilution developed can perhaps be understood by considering the origin of the fluid that appeared in the circulation of hypotensive patients. Several possibilities exist. Hypovolaemia is capable of recruiting appreciable amounts of fluid from skeletal muscle and skin [11], but this is not consistent with the essentially unchanged Hb concentration when extradural anaesthesia is induced in the absence of volume loading [1].

Another potential source of the fluid is the interstitial fraction of Ringer's acetate solution infused during the first 20 min of the study. "Autotransfusion" with interstitial fluid, is a rapid process if the capillary pressure is lowered [11] and can hardly explain the delay in haemodilution. This mechanism does operate to some degree, however, as evidenced in a few patients in whom volume loading was terminated just before the local anaesthetic was injected.

A third possibility is that the fluid for increased haemodilution is derived mainly from the ongoing infusion. This view serves best to explain the 15-min delay between hypotension and haemodilution. It also receives support from a recent study in which hypotension promoted a deviation in blood glucose concentration towards the glucose concentration of the crystalloid infusion (being 0 to 0.5%), thus indicating excess enrichment of the ongoing infusion in the blood of hypotensive patients [12].

The use of a local anaesthetic solution that contained adrenaline is not likely to have affected the hypotension–haemodilution relationship found in this study [1]. Absorption of adrenaline may explain the tachycardia observed just after the induction, while block of cardiac sympathetic fibres by high-level analgesia can account for the difference in heart rate between the hypotensive and normotensive patients. Adrenaline can probably also account for the mild transient haemoconcentration observed after the local anaesthetic solution had just been injected.

Atrial natriuretic peptide released during initial volume loading is a possible factor augmenting hypotension by reducing vascular tone and increasing vascular permeability [13, 14]. Such an effect could not be discerned statistically, however, as pronounced volume expansion before extradural anaesthesia did not correlate with hypotension.

One should be aware of the artificial division between patients who showed a decrease in systolic AP of more or less than 25%. However, a reduction in systolic AP to a predetermined physiological level, such as < 100 mm Hg or a decrease of 20–30% below baseline, appears to be conventional in this type of study [15]. The categorical approach was used here only to achieve the highest possible degree of clarity in the presentation. Figure 3 shows that the hypotension–haemodilution relationship is in fact a continuous linear function, and our slope agreed well with those of previous reports [1–3].

References

1. Hahn RG. Haemoglobin dilution from epidural-induced hypotension with and without fluid loading. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 241–244.
2. Hahn RG. Blood volume at the onset of hypotension in TURP performed during epidural anaesthesia. *European Journal of Anaesthesiology* 1993; **10**: 219–225.
3. Hahn RG. Increased haemodilution in hypotension induced by epidural anaesthesia. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 357–360.
4. Kempen PM, Tick RC. Hemodilution, regional block and Cesarean section. *Regional Anesthesia* 1990; **15** (1S): 9.
5. Retzlaff JA, Tauxe WN, Kiely JM, Stroebel CF. Erythrocyte volume, plasma volume, and lean body mass in adult men and women. *Blood* 1969; **33**: 649–667.
6. Mark JB, Steele SM. Cardiovascular effects of spinal anesthesia. *International Anesthesiology Clinics* 1989; **27**: 31–53.
7. Arndt JO, Höck A, Stanton-Hicks M, Stühmeier K-D. Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* 1985; **63**: 616–623.
8. Coe AJ, Revenäs B. Is crystalloid preloading useful in spinal anaesthesia in the elderly? *Anaesthesia* 1990; **45**: 241–243.
9. Nishimura N, Kajimoto Y, Kabe T, Sakamoto A. The effects of volume loading during epidural anaesthesia. *Resuscitation* 1985; **13**: 31–39.

10. Rocke DA, Rout CC. Volume preloading, spinal hypotension and Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 257–259.
11. Länne T, Lundvall J. Very rapid net transcapillary fluid absorption from skeletal muscle and skin in man during pronounced hypovolaemia circulatory stress. *Acta Physiologica Scandinavica* 1989; **136**: 1–6.
12. Hahn RG. Origin of intravascular fluid recruited by vasodilatation during epidural anaesthesia. *European Surgical Research* 1996; **28**: 70–74.
13. Kampe-Jensen M, Olesen KL, Back V, Schütten HJ, Engqvist A. Changes in serum electrolytes and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic and Ringer lactate solution in healthy volunteers. *British Journal of Anaesthesia* 1990; **64**: 606–610.
14. Carvalho JCA, Matjias RS. Intravenous hydration in obstetrics. *International Anesthesiology Clinics* 1994; **32**: 103–115.
15. McCrae AF, Wildsmith JAW. Prevention and treatment of hypotension during central neural block. *British Journal of Anaesthesia* 1993; **70**: 672–680.

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LABORATORY INVESTIGATIONS

Combination of inhaled nitric oxide with i.v. nitroglycerin or with a prostacyclin analogue in the treatment of experimental pulmonary hypertension

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Summary

We have studied the effect of combining inhaled nitric oxide (NO) with an i.v. vasodilator agent, nitroglycerin, or ciloprost, a prostacyclin analogue, during acute pulmonary hypertension in pigs, induced by continuous infusion of a thromboxane analogue (U46619), adjusted to maintain mean pulmonary artery pressure (MPAP) at 40 mm Hg. The effects of the different treatments on MPAP and pulmonary resistances were determined. In the first part of the study, we determined the dose–response to increased NO concentrations from 5 to 40 ppm. This showed a maximum pulmonary effect with NO 5 ppm, but with no systemic effects. The effect of NO 10 ppm was then compared with two i.v. drugs. Nitroglycerin was less effective than NO on pulmonary vessels but induced significant arterial hypotension. Pulmonary vasodilatation induced by ciloprost was greater than that by NO but with the same side effects as nitroglycerin on systemic variables. We also found that the combination of NO and nitroglycerin had the same pulmonary effects as NO 10 ppm but that adding ciloprost to NO decreased pulmonary pressures significantly more than either drug used alone. We conclude that inhaled NO may be usefully combined with i.v. ciloprost but not with i.v. nitroglycerin. (*Br. J. Anaesth.* 1996; **77**: 227–231)

Key words

Complications, pulmonary hypertension. Pharmacology, nitric oxide. Pharmacology, nitroglycerin. Hormones, prostaglandins. Pig.

Pulmonary vasoconstriction after cardiopulmonary bypass should be treated rapidly as it causes right ventricular failure [1]. Under normal physiological conditions, the endothelium maintains low pulmonary vascular resistances by producing two potent vasodilators, endothelium-derived relaxing factor (EDRF) and prostacyclin [2]. The effect of these two substances is similar: they relax vascular smooth muscle, although via different pathways. Prostacyclin stimulates adenylate cyclase thus increasing cAMP concentrations [3]. This second messenger activates cAMP-dependent protein kinase to modify phosphorylation of myosin and relax smooth muscle. In contrast, EDRF (which is nitric oxide) stimulates cytoplasmic guanylate cyclase increasing cyclic guanosine monophosphate (cGMP) concentration, which is another second messenger that relaxes vascular smooth muscle, after activation of cGMP-dependent protein kinase. The endothelial cell, therefore, plays a crucial role in the control of pulmonary vascular tone, as reviewed recently by Loscalzo [4].

The inflammatory response initiated by cardiopulmonary bypass activates the granulocytes and their secretion of oxygen radicals damages the endothelial cell, thus contributing to the development of pulmonary hypertension [5]. The release of thromboxane A_2 by platelets and the heparin–protamine reaction further complicate this situation [6]. It has also been shown that the response to a thromboxane analogue (U46619) is increased for 2 days after experimental cardiopulmonary bypass in dogs [7]. Nitrates, prostacyclin or, more recently, inhaled nitric oxide (NO) [8] have been used successfully to treat this acute complication. Recently, it has been reported that inhaled NO associated with prostacyclin could have a synergistic effect in the treatment of pulmonary hypertension associated with correction of a congenital aortic stenosis [9].

Therefore, in this study, we determined if combining inhaled NO with either i.v. nitroglycerin or i.v. ciloprost, a synthetic analogue of prostacyclin (PGI_2), would enhance the pulmonary vasodilator effect.

Materials and methods

This study was approved by our Institutional Research and Animal Welfare Committee. All animals were treated according to the Canadian Animal Protective Council Guidelines.

Female pigs, weighing 20–25 kg, were anaesthetized with ketamine 15 mg kg^{-1} i.m. After a bolus of fentanyl 5 $\mu g\ kg^{-1}$, ventilation was controlled mechanically via a tracheostomy.

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Tidal volume was set at 15 ml kg^{-1} and the frequency adjusted to maintain Pa_{CO_2} at 4.6–6.0 kPa. FI_{O_2} was maintained at 30%. Anaesthesia was maintained with infusions of fentanyl and pentobarbitone; to decrease its cardiovascular effects, pancuronium was combined with tubocurarine to provide neuromuscular block. Lactated Ringer's solution was infused at 15 ml h^{-1}.

Mean systemic arterial pressure (MAP) was recorded via the carotid artery. A pulmonary artery catheter (5-French gauge) was introduced into the pulmonary artery via the internal jugular vein. Catheters (12-French gauge) were inserted by sternotomy into the main pulmonary artery and into the left atrium to record, respectively, mean pulmonary artery pressure (MPAP) and left atrial pressure (LAP). All pressures were measured with Abbot (Abbott, Montreal, PQ, Canada) transducers. Cardiac output was recorded as the average of three thermodilution measurements obtained after injection of saline 5 ml kept at 4 °C.

Inhaled NO was provided by adding a mixture of NO and nitrogen to the air entry of a Puritan Bennett 1200AE respirator. NO concentrations were measured by chemiluminescence (TECAN ciloprost D 700AL analyser, AMKO Inc., Ontario, Canada), sampling in the inspiratory limb of the respiratory circuit.

The animal was allowed to stabilize for 30 min after surgery, after which pulmonary hypertension was induced by continuous infusion of a thromboxane analogue (U 46619: Upjohn, Kalmazoo, MI, USA) at 20 µg ml^{-1} diluted in 0.9% saline into a separate vein in the ear. The infusion rate was adjusted to maintain a stable MPAP of 40 mm Hg for 20 min.

DETERMINATION OF THE DOSE–RESPONSE CURVE TO NITRIC OXIDE

To determine the optimum inhaled NO concentration to be used during comparisons with the i.v. drugs, we established a dose–response curve for NO in our model by increasing the NO concentration from 5 to 40 ppm. Each experiment was therefore separated into seven periods of 20 min starting when a stable condition was observed for at least 10 min after any therapeutic modification: (1) basal status; (2) pulmonary hypertension as described above; (3) inhaled NO concentration set at 5 ppm; (4) at 10 ppm; (5) at 20 ppm; (6) at 40 ppm; and (7) return to the second stage discontinuing NO.

The inhaled NO concentration was increased cumulatively. Haemodynamic variables (MAP, MPAP, LAP, CO) were recorded every 5 min during each period. Seven pigs were included in this preliminary study.

COMPARISON BETWEEN THE EFFECT OF NO 10 PPM AND THE MAXIMUM EFFECT OF EITHER NITROGLYCERIN OR PROSTACYCLIN INFUSION

Pulmonary hypertension was initiated in 14 pigs as described previously and treated for 20 min with 10 ppm of inhaled NO, which was then stopped to allow recovery of pulmonary hypertension. The animal was then allocated randomly to receive either an infusion of nitroglycerin 400 µg ml^{-1} diluted in 5% glucose ($n = 7$) or an infusion of ciloprost (Iloprost, Berlex, St Laurent, PQ, Canada) 10 µg ml^{-1} diluted in 0.9% saline ($n = 7$). These infusions via the jugular vein were started with nitroglycerin 1 µg kg^{-1} min^{-1} or ciloprost 0.1 µg kg^{-1} min^{-1} and increased progressively until we observed either a return of MPAP to basal values or a 20% reduction in basal MAP. When this occurred, the infusion was kept constant for 20 min to record haemodynamic variables and arterial blood-gas tensions. After this period, NO 10 ppm was reintroduced for 20 min to assess any beneficial effect of the combination of the two drugs. All treatments were then discontinued to restore pulmonary hypertension.

Pulmonary (PVR) and systemic (SVR) vascular resistances were calculated, respectively, according to the formulae:

$$(\text{MPAP} - \text{LAP})/\text{CO} \times 79.9 \text{ and}$$
$$(\text{MAP} - \text{CVP})/\text{CO} \times 79.9$$

All data are presented as mean (SEM). Statistical analysis comprised analysis of variance for repeated measures. Bonferroni's method was used for *post hoc* multiple comparison when analysis of variance was significant. $P \leqslant 0.05$ was considered significant.

Results

Data recorded during determination of the dose–response to inhaled NO are summarized in table 1. MPAP and PVR were increased significantly by U46619 compared with baseline values. However, there were no changes in MAP and SVR after infusion of the thromboxane analogue.

The dose–response curve to inhaled NO 5–40 ppm showed a maximum effect on pulmonary artery pressure at the 5 ppm concentration; increasing NO concentration did not alter significantly either MPAP or PVR compared with the initial concentration. From this dose–response curve and as the effect of inhaled NO reached a plateau starting at 5 ppm, a concentration of 10 ppm of inhaled NO was chosen as supramaximal stimulation to evaluate its effect when combined with the i.v. drugs.

In the second part of the study, when a constant dose of NO 10 ppm was inhaled, pulmonary artery pressure decreased by 29 (2)% in the group receiving nitroglycerin and by 27 (3)% in the group receiving ciloprost, while PVR decreased by 44 (4)% in the nitroglycerin group and by 49 (5)% in the ciloprost group.

Data recorded in the nitroglycerin group are summarized in table 2 and those in the ciloprost group in table 3, while table 4 shows the effect of different treatments for pulmonary hypertension on MPAP and PVR. The decrease induced by treatment is expressed as a percentage of the value recorded during pulmonary hypertension.

The mean maximal dose of nitroglycerin infused was 2.5 (0.15) µg kg^{-1} min^{-1}, while for ciloprost it was 0.32 (0.02 µg kg^{-1} min^{-1}. Nitroglycerin infusion

Table 1 Data recorded during treatment of pulmonary hypertension with inhaled NO at increasing concentrations from 5 to 40 ppm (mean (SEM)). Basal = values recorded 30 min after surgery before any intervention; U 46619 values recorded after induction of pulmonary hypertension with U 46619. NO 5 ppm = values recorded when inhaled NO was set at 5 ppm; NO 10 ppm = values recorded when inhaled NO was set at 10 ppm; NO 20 ppm = values recorded when inhaled NO was set at 20 ppm NO; NO 40 ppm = values recorded when inhaled NO was set at 40 ppm. MAP = mean systemic arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = mean central venous pressure; LAP = mean left atrial pressure. *$P < 0.05$ compared with basal values; †$P < 0.05$ compared with U 46619

	Basal ($n = 7$)	U 46619 ($n = 7$)	NO 5 ppm ($n = 7$)	NO 10 ppm ($n = 7$)	NO 20 ppm ($n = 7$)	NO 40 ppm ($n = 7$)
MAP (mm Hg)	109 (7.7)	119 (9.1)	119 (9.3)	120 (8.9)	120 (7.2)	120 (5.6)
CO (litre min^{-1})	3.3 (0.4)	3.4 (0.4)	3.6 (0.4)	3.6 (0.4)	3.7 (0.4)	3.9 (0.5)
CVP (mm Hg)	8.0 (0.9)	11.0 (1.6)	11.2 (1.7)	10.7 (1.5)	11.0 (1.4)	10.9 (1.5)
LAP (mm Hg)	9.4 (1.0)	10.8 (1.6)	11.2 (1.7)	10.7 (1.5)	11.0 (1.4)	10.9 (1.5)
MPAP (mm Hg)	20.8 (1.4)	39.4 (0.5)*	31.4 (1.0)*†	29.5 (1.2)*†	29.0 (1.4)*†	28.0 (1.0)*†
PVR (dyn s cm^{-5})	267 (41)	694 (56)*	459 (43)*†	436 (45)*†	422 (50)*†	361 (36)*†
SVR (dyn s cm^{-5})	2502 (237)	2619 (222)	2522 (266)	2556 (266)	2587 (316)	2464 (308)

Table 2 Data recorded during treatment of pulmonary hypertension with inhaled NO 10 ppm, nitroglycerin or their combination (mean (SEM)). Basal = values recorded 30 min after surgery before any intervention; U 46619 = values recorded after induction of pulmonary hypertension with U 46619. NO 10 ppm = values recorded when inhaled NO was set at 10 ppm; NTG = values recorded during nitroglycerin infusion; NO–NTG = values recorded during infusion of nitroglycerin and inhaled NO 10 ppm; MAP = mean systemic arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = mean central venous pressure; LAP = mean left atrial pressure. *$P < 0.05$ compared with U 46619; †$P < 0.05$ compared with NO 10 ppm

	Basal ($n = 7$)	U 46619 ($n = 7$)	NO 10 ppm ($n = 7$)	NTG ($n = 7$)	NO–NTG ($n = 7$)
MAP (mm Hg)	121 (7)	127 (9)	127 (8)	95 (8)*†	98 (6)*†
CO (litre min^{-1})	3.19 (0.3)	3.2 (0.8)	3.1 (1.1)	3.2 (1.0)	3.3 (0.5)
CVP (mm Hg)	6.2 (0.6)	7.7 (0.8)	6.8 (0.6)	6.1 (0.7)	6.3 (0.5)
LAP (mm Hg)	9.6 (1.5)	10.7 (2.0)	10.8 (1.6)	9.6 (1.7)	9.7 (1.7)
MPAP (mm Hg)	22.1 (0.5)	39.9 (0.5)	28.1 (0.7)*	31.4 (0.5)*†	27.1 (1.0)*
PVR (dyn s cm^{-5})	344 (26)	793 (70)	453 (47)*	617 (84)*†	449 (47)*
SVR (dyn s cm^{-5})	2911 (152)	3211 (402)	3183 (176)	2565 (283)*†	2466 (324)*†
Pa_{O_2} (kPa)	13.9 (1.4)	12 (1.3)	15.3 (1.5)*	12.4 (1.6)	13.8 (1.6)

Table 3 Data recorded during treatment of pulmonary hypertension with inhaled NO 10 ppm, prostacyclin or their combination (mean (SEM)). Basal = values recorded 30 min after surgery before any intervention; U 46619 = values recorded after induction of the pulmonary hypertension with U 46619. NO 10 ppm = values recorded when inhaled NO was set at 10 ppm; CL = values recorded during prostacyclin (ciloprost) infusion; NO–CL = values recorded during infusion of prostacyclin and NO 10 ppm; MAP = mean systemic arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = mean central venous pressure; LAP = mean left atrial pressure. *$P < 0.05$ compared with U 46619; †$P < 0.05$ compared with NO 10 ppm; ‡$P < 0.05$ NO–CL *vs* CL

	Basal ($n = 7$)	U 46619 ($n = 7$)	NO 10 ppm ($n = 7$)	CL ($n = 7$)	NO–CL ($n = 7$)
MAP (mm Hg)	109 (5)	110 (6)	107 (6)	99 (5)*†	98 (6)*†
CO (litre min^{-1})	2.53 (0.6)	2.2 (0.2)	2.3 (0.2)	2.8 (0.3)	2.8 (0.5)
CVP (mm Hg)	7.2 (0.6)	8.6 (0.8)	7.6 (0.8)	7.4 (0.6)	6.8 (0.8)
LAP (mm Hg)	14.2 (1.9)	16.5 (2.0)	16.1 (2.0)	15.4 (1.9)	15.7 (2.0)
MPAP (mm Hg)	24.5 (1.4)	43.2 (1.5)	30.8 (1.2)*	25.0 (1.2)*†	22.7 (1.5)*‡
PVR (dyn s cm^{-5})	414 (63)	1102 (166)	534 (94)*	327 (72)*†	211 (60)*‡
SVR (dyn s cm^{-5})	3325 (315)	3910 (185)	3729 (176)	2793 (283)*†	2743 (324)*†
Pa_{O_2} (kPa)	15.3 (1.4)	12.3 (1.4)	15.3 (1.3)*	13.7 (1.5)	13.8 (1.5)

Table 4 Variations in pulmonary pressures (MPAP) and resistances (PVR). The decrease induced by treatment is expressed as a percentage of the value recorded during the pulmonary hypertension stage. NO 10 ppm = effect of 10 ppm inhaled NO; drug = effect of the i.v. drug, either nitroglycerine (NTG) or ciloprost (CL); NO–drug = effect of the combination of the i.v. drugs with 10 ppm inhaled NO. *$P < 0.05$ compared with NO 10 ppm; †$P < 0.05$ compared with drug

	MPAP			PVR		
	NO 10 ppm	Drug	NO–Drug	NO 10 ppm	Drug	NO–Drug
Group NTG	−44 (4)	−22 (6)*	−43 (2)†	−29 (2)	−29 (2)	−31 (2)
Group CL	−49 (5)	−70 (4)*	−81 (4)*†	−27 (3)	−39 (2)*	−47 (4)*†

alone decreased MPAP and PVR, respectively, by 29 (2)% and 22 (6)% (table 2). For ciloprost infusion alone, MPAP was decreased by 39 (3)% and PVR by 70 (4)%. Hence, the variations induced by infusion of ciloprost were significantly greater for both MPAP and PVR than those produced by nitroglycerin.

Comparing the variations induced by inhaled NO alone with those induced by the combination of inhaled NO and nitroglycerin, there were no significant differences for either MPAP or PVR. The effects observed with the combination of inhaled NO and ciloprost were, however, significantly greater for MPAP and PVR than those recorded when only inhaled NO was provided. This combination was also significantly more effective on these variables than when ciloprost alone was infused.

We found that MAP and SVR were not altered significantly by inhaled NO. Infusion of nitroglycerin, however, decreased MAP by 25 (4)% and SVR by 22 (4)% while they decreased by 10 (4)% and 30 (7)%, respectively, with infusion of ciloprost. The combination of inhaled NO with either of the two i.v. agents did not alter significantly MAP or SVR.

Return to baseline MPAP was seen in one of seven pigs treated with nitroglycerin and in five of seven pigs when ciloprost was infused. This suggests that the decrease in SAP was the limiting factor for the increase in infusion in six pigs in the nitroglycerin group and in two pigs in the ciloprost group, these values being significantly different (Fisher's exact test: $P = 0.029$).

In both groups only inhaled NO improved Pa_{O_2} significantly compared with values obtained during pulmonary hypertension (tables 2, 3).

Discussion

In the first part of this study, we confirmed the effectiveness and selectivity of inhaled NO as a pulmonary vasodilator. A concentration of 5 ppm significantly decreased pulmonary pressure with no effect on systemic variables, as described previously by Frostell and colleagues [10]. We also observed that in our model of pulmonary hypertension induced by a thromboxane analogue, increasing the inhaled NO concentration from 5 to 40 ppm did not significantly increase pulmonary vasodilatation.

Our second set of experiments showed that ciloprost appeared to be more effective than inhaled NO or nitroglycerin in reducing pulmonary hypertension while inhaled NO in combination with i.v. nitroglycerin did not enhance its efficacy. In contrast, the combination of inhaled NO and i.v. ciloprost revealed some additive effect of these two drugs.

Nitroglycerin is an i.v. drug used commonly to treat pulmonary hypertension. The use of i.v. nitrovasodilatators is, however, often limited by systemic effects. Inhaled NO has the unique advantage of pulmonary selectivity as it is rapidly inactivated because it is bound tightly to haemoglobin [11]. Moreover, being distributed only to the ventilated regions of the lung, inhaled NO reduces intrapulmonary shunting, as shown by the increase in Pa_{O_2}. The i.v. vasodilators increase venous admixture which normally results in a decrease in Pa_{O_2} [12], but our study did not show this side effect, probably because most of our pigs were free from chest disease and intrapulmonary shunt was minimal [13].

Nitroglycerin acts only after intracellular release of NO [14], which implies that these two drugs share the same mechanism of action via activation of the cGMP pathway. Our study suggests that relaxation of the vascular smooth muscle cell by cGMP reaches a plateau, which was achieved in our model with 5 ppm of inhaled NO. This was confirmed further by the fact that adding another i.v. drug which acts via the same pathway did not increase pulmonary vascular dilatation.

Prostacyclin is the other i.v. drug used widely to treat primary or secondary pulmonary hypertension in adults and children [15]. Recently, its aerosolized form has been administered successfully for the treatment of pulmonary hypertension in an animal model [16] and in children suffering from acute respiratory syndrome [17]. Two synthetic analogues with short half-lives have been developed: epoprosterenol and ciloprost. They produce the same pharmacological activities of natural prostacyclin, including peripheral vasodilatation, inhibition of platelet aggregation and some cytoprotection. These compounds bind to membrane prostacyclin receptors and stimulate adenylate cyclase. The subsequent increase in cAMP concentration relaxes smooth muscle. It has also been suggested that prostacyclin hyperpolarizes the membrane of the smooth muscle cell to produce relaxation.

In our study, we observed that ciloprost reversed induced pulmonary hypertension more frequently than nitroglycerin. This does not imply that ciloprost is more powerful than nitroglycerin but that ciloprost has greater pulmonary selectivity, which was confirmed by the fact that the progressive increase in the i.v. infusion was not limited as frequently by systemic hypotension in the ciloprost group compared with the nitroglycerin group; another explanation may be improved cardiac contractility secondary to the increase in the intracellular cAMP concentration, while NO and cGMP have negative inotropic actions [18].

We found a cumulative effect of ciloprost and inhaled NO on the decrease in MPAP and PVR. The synergistic action between NO and ciloprost has been demonstrated previously on isolated coronary arteries, in which PGI_2 relaxation was potentiated by the presence of the vascular endothelium [19]. This effect has also been shown in the hamster microcirculation where the combination of drugs increasing cAMP and drugs increasing cGMP were more effective than either drug alone [20]. This may be explained by the fact that NO activates the GMP pathway whereas ciloprost stimulates adenylate cyclase and the AMP pathway. The combination of NO and ciloprost has been reported to be useful in some case reports [9] but a careful assessment of the benefit of this association has not yet been reported.

References

1. Vlahakes GJ, Turley K, Hoffman JIE. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. *Circulation* 1981; **63**: 87–95.
2. Dinh-Xuan AT. Endothelial modulation of pulmonary vascular tone. *European Respiratory Journal* 1992; **5**: 757–762.

3. Kerins DM, Murray R, Fitzgerald GA. Prostacyclin and prostaglandin E_1: molecular mechanism and therapeutic utility. *Progress in Hemostasis and Thrombosis* 1991; **10**: 307–337.
4. Loscalzo J. Endothelial dysfunction in pulmonary hypertension. *New England Journal of Medicine* 1992; **327**: 117–119.
5. Kirklin JK, George JF, Holman W. The inflammatory response to cardiopulmonary bypass. In: Gravlee GP, Davis RF, Utley JR, eds. *Cardiopulmonary Bypass: Principles and Practice.* Baltimore: Williams and Wilkins, 1993; 233–248.
6. Lowenstein E, Zapol WM. Protamine reactions, explosive mediator release and pulmonary vasoconstriction. *Anesthesiology* 1990; **73**: 373–375.
7. Nyhan D, Redmond J, Gillinov M, Nishiwaki K, Murray P. Prolonged pulmonary vascular hyperreactivity in conscious dogs after cardiopulmonary bypass. *Journal of Applied Physiology* 1994; **77**: 1584–1590.
8. Linberg L, Larsson A, Steen S, Olsson SG, Nordström L. Nitric oxide gives maximal response after coronary artery bypass surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 1994; **8**: 182–187.
9. Schranz D, Huth R, Wippermann CF, Ritzerfeld S, Schmitt F, Oelert H. Nitric oxide and prostacyclin lower suprasystemic pulmonary hypertension after cardiopulmonary bypass. *European Journal of Pediatrics* 1993; **152**: 793–796.
10. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991; **83**: 2038–2047.
11. Rimar S, Gillis CN. Selective pulmonary vasodilatation by inhaled nitric oxide is due to hemoglobin inactivation. *Circulation* 1993; **88**: 2884–2887.
12. Rademacher P, Santak B, Wüst H, Tarnow J, Falke K. Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: effects on pulmonary capillary pressure and ventilation perfusion distributions. *Anesthesiology* 1990; **72**: 238–244.
13. Hannon J, Bossone C, Wade C. Normal physiological values for conscious pigs used in biomedical research. *Laboratory Animal Science* 1990; **43**: 293–298.
14. Salvemini D, Pistelli A, Vane J. Conversion of glyceryl trinitrate to nitric oxide in tolerant and non-tolerant smooth muscle and endothelial cells. *British Journal of Pharmacology* 1993; **108**: 162–169.
15. Bush A, Busst C, Knight WB, Shinebourne EA. Modification of pulmonary hypertension secondary to congenital heart disease by prostacyclin therapy. *American Review of Respiratory Disease* 1987; **136**: 767–769.
16. Welte M, Zwissler B, Habazettl H, Messmer K. PGI_2 aerosol versus nitric oxide for selective pulmonary vasodilatation in hypoxic pulmonary vasoconstriction. *European Surgical Research* 1993; **25**: 329–340.
17. Pappert D, Bush T, Gerlach H, Lewandowski K, Radermacher P, Rossaint R. Aerosolized prostacyclin versus inhaled nitric oxide in children with severe acute respiratory distress syndrome. *Anesthesiology* 1995; **82**: 1507–1511.
18. Brady AJ, Warren JB, Poole Wilson PA, Williams TJ, Harding SE. Nitric oxide attenuates cardiac myocytes contraction. *American Journal of Physiology* 1993; **265**: H176–182.
19. Shimokowa H, Flavahan N, Lorenz R, Vanhoutte P. Synergistic interaction between prostacyclin and endothelium derived relaxing factor in porcine coronary arteries. In Rubanyi GM, Vanhoutte PM, eds. *Endothelium-derived Relaxing Factors.* Basel: Karger, 1990; 303–308.
20. De Wit C, von Bismark P, Pohl U. Synergistic action of vasodilators that increase cGMP and cAMP in the hamster cremaster microcirculation. *Cardiovascular Research* 1994; **28**: 1513–1518.

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Role of prostaglandins and nitric oxide on halothane-induced arteriolar dilatation in rat diaphragm

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Summary

The effects of anaesthetics on the microcirculation of the diaphragm are incompletely understood. Therefore, we assessed by *in vivo* intravital microscopy in rats the action of halothane on diaphragmatic arteriolar diameter and the role of nitric oxide and prostaglandins on halothane-induced diaphragmatic arteriolar diameter. We studied 54 rats anaesthetized with thiopentone. Dose–response curves to topically applied Krebs' solution saturated with halothane at increasing concentrations of 0%, 1%, 3% and 5% were carried out in the presence of an inhibitor of nitric oxide synthesis (*N*ω-nitro-L-arginine (LNA), 300 μmol litre^{-1}) or inhibitors of prostaglandin synthesis (mefenamic acid 20 μmol litre^{-1} or indomethacin 20 mol litre^{-1}) or in the absence of any inhibitor. We found dose-dependent arteriolar dilatation which was abolished by mefenamic acid and indomethacin. In contrast, the effect of halothane was not modified by LNA. These data demonstrated that halothane-induced arteriolar dilatation in the diaphragm of the rat was mediated by prostaglandins but not by nitric oxide. (*Br. J. Anaesth.* 1996; **77**: 232–237)

Key words

Anaesthetics volatile, halothane. Hormones, prostaglandins. Pharmacology, nitric oxide. Muscle respiratory. Rat.

Halothane is commonly considered as a pure vasodilator. However, animal and human studies *in vivo* have shown that halothane has different effects in vascular beds [1–3]. Miller, Kistner and Epstein [2] showed in rats that inhalation of halothane induced an increase in blood flow to the brain, kidney and liver, and a decrease in blood flow to the heart and peripheral and respiratory skeletal muscles. In a previous work we showed that inhalation of halothane was unable to dilate the arterioles of the diaphragm [4]. These differences in vascular responses to inhalation of halothane observed *in vivo* may be related to differences in the sensitivity of vascular beds to this agent [5]. Alternatively, they may reflect differences in local vascular adaptation to the haemodynamic changes induced by halothane. Therefore, we assessed the vascular effects of halothane on diaphragmatic microcirculation.

In this study we assessed the direct effects of halothane on diaphragmatic arteriolar diameters, by topical administration on the surface of the diaphragm in order to avoid its systemic haemodynamic action and evaluated the mechanism(s) of action of halothane on diaphragmatic arterioles. We were interested in the role of the vascular endothelium because it has been shown recently that halothane modulates endothelium-dependent relaxation [6]. Therefore, we assessed the role of endothelial agents, such as nitric oxide and prostaglandins, on halothane-induced diaphragmatic arteriolar diameter by inhibition of nitric oxide synthesis with *N*ω-nitro-L-arginine (LNA) [7, 8] and prostaglandin synthesis with mefenamic acid or indomethacin [9]. Special emphasis was placed on evaluation of the effects of prostaglandins, as these agents contribute, together with nitric oxide, to modulation of diaphragmatic arteriolar tone [10], a phenomenon which could not be detected in other skeletal muscle microvessels [11, 12].

Materials and methods

Male Sprague–Dawley rats weighing 163 (5) g were anaesthetized with sodium pentobarbitone 50 mg/kg body weight i.p. A patent airway was maintained with a tracheostomy tube and the lungs were ventilated throughout the study with a rodent ventilator (Ugo Basile Apparatus Inc., Italy) at an $F_{I_{O_2}}$ of 0.5. The left carotid artery was cannulated for continuous arterial pressure monitoring with a Statham P23 DB transducer. All animals whose mean arterial pressure decreased to less than 90 mm Hg were excluded from the study. The right jugular vein was cannulated for administration of 5 ml kg^{-1} normal saline during surgery. Body temperature was monitored continuously with a rectal

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probe and maintained constant at 36.5–37.5 °C by a heat lamp and a heating pad (Harvard Apparatus, MA, USA).

The experimental design was in agreement with the recommendations of French Law (Ministère des Affairs Sociales et de la Solidarité Nationale) and all experiments were approved by the local Animal Committee.

PREPARATION OF THE DIAPHRAGM

The diaphragm preparation has been described in detail previously [10, 13]. Briefly, a bilateral thoracotomy was performed in the fifth intercostal space, the sternum remaining intact. The diaphragm was separated carefully from the lungs and the mediastinal tissues. A midline laparotomy was followed by a transverse incision at each side which allowed exposure of the diaphragm in a perpendicular position relative to the body of the animal. The animal was placed in a Trendelenburg position on a rodent operating table (Harvard Apparatus, MA, USA).

When the diaphragm was exposed, its abdominal face was irrigated continuously with a modified Krebs–Henseleit solution containing (mmol litre^{-1}): NaCl 118, KCl 5.9, $CaCl_2$–$2H_2O$ 2.5, $MgSO_4$–$7H_2O$ 0.5, $NaHCO_3$ 28 and glucose 10. This solution was maintained at 37.5 °C and pH, $P\text{O}_2$ and $P\text{CO}_2$ were, respectively, fixed at 7.41 (0.06), 3.1 (0.2) kPa and 5.5 (0.1) kPa by bubbling with a 5 % carbon dioxide–95 % nitrogen gas mixture. Pancuronium 4 μmol litre^{-1} was added to Krebs' solution to prevent muscle fasciculation.

The muscle was transilluminated using a 150-W tungsten–halogen lamp connected to a fibreoptic cold light microprobe introduced gently through the left thoracotomy aperture. The diaphragmatic microcirculation was observed with a modified Leitz microscope placed in a position parallel to the area of the abdominal side of the muscle. The image, magnified by a 20 × long-distance objective, was projected into a CCD video camera (Sony DXC-101P) connected to a videotape recorder (Sony VO-9600 P) and a video monitor (Sony PVM-1371 QM). Total magnification from the vessel image to the monitor was × 600. Arteriolar diameters were measured by playback analysis of the video record using the technique of Intaglietta and Tompkins [14] and, after completion of the experimental procedures, the microvascular images were read by one of the investigators who was blinded to the sequence of experimental steps.

We studied changes in the diameter of the arteriolar branches arising from the internal mammary and intercostal arteries. Second and third arteriolar orders (A2 and A3, respectively) were analysed according to the number of bifurcations proximal to the studied arterioles, as described previously [15]. Only clearly distinguishable vessels were selected and the number of measured arterioles varied between one and three of each order per preparation. Before any measurement, a 20–30-min period after surgery was allowed to reach a steady state of arteriolar tone.

EXPERIMENTAL DESIGN

Two studies were performed.

Study 1

In seven animals arteriolar diameter was measured at baseline and then Krebs' solution saturated with increasing concentrations (0 %, 1 %, 3 % and 5 %) of halothane was applied topically in order to perform a cumulative dose–response curve. The different concentrations were administered in a stepwise manner for 2 min each. The diameter of the selected arteriole was measured at the end of each administration. This was followed by a 15-min wash-out period during which the muscle was irrigated with drug-free Krebs' solution. At the end of this period, the diameter of the same arterioles studied previously was measured and a second cumulative dose–response curve to halothane was performed in order to evaluate the reversibility of the effects of halothane.

Study 2

Twenty-eight animals were allocated to one of four groups according to topical administration on the diaphragm of Krebs' solution containing LNA 300 μmol litre^{-1} ($n = 7$ animals, group LNA), mefenamic acid 20 μmol litre^{-1} ($n = 7$ animals, group MA), indomethacin 20 μmol litre^{-1} ($n = 7$) or no inhibitor ($n = 7$ animals, group C). Diameter was measured at baseline and after a 20-min superfusion period. Then, Krebs' solution saturated with increasing concentrations (0 %, 1 %, 3 % and 5 %) of halothane was applied topically in order to perform a cumulative dose–response curve, as described above. The inhibitors corresponding to each pretreatment group were also present in the halothane-saturated Krebs' solutions. The diameter of the selected arteriole was measured at the end of each application.

DOSE OF HALOTHANE

Samples of Krebs' solution equilibrated with halothane were removed at the end of an application period for subsequent measurement of anaesthetic concentration in Krebs' solution by gas chromatography [16].

REAGENTS

Halothane was obtained from Laboratoires Belamont (Paris, France) and was introduced into 40 ml of Krebs' solution at 37 °C by bubbling with 5 % carbon dioxide–95 % nitrogen passed through a precalibrated vaporizer (flow 0.5 litre min^{-1}) for 15 min. Vaporizers delivered halothane at 0 %, 1 %, 3 % and 5 %. Mefenamic acid and LNA were obtained from Sigma Chemical Co. (St Louis, MO, USA). Mefenamic acid was dissolved in sodium carbonate 1 mg ml^{-1} and diluted to the final concentration with Krebs' solution. LNA was dissolved directly in

Krebs' solution by stirring at room temperature. Indomethacin was obtained from Merck, Sharp and Dohme Chibret Products, France. Drug solutions were prepared freshly daily.

STATISTICAL ANALYSIS

All results are expressed as mean (SD). Comparison between arteriolar diameters at baseline in the different groups of animals was performed by one-way analysis of variance. Evaluation of the effects of each inhibitor on baseline arteriolar diameter was performed by a paired *t* test. Comparison between arteriolar dose–response curves (diameter *vs* dose of halothane) between the different groups of animals was performed using two-way analysis of variance for repeated measures, one "within" factor, that is factor "dose" and a grouping factor "absence or presence of inhibitor" [17]. $P < 0.05$ was considered significant.

Results

The experimental interventions did not affect systemic arterial pressure, which was stable over the course of the experiments and within the range 95–120 mm Hg.

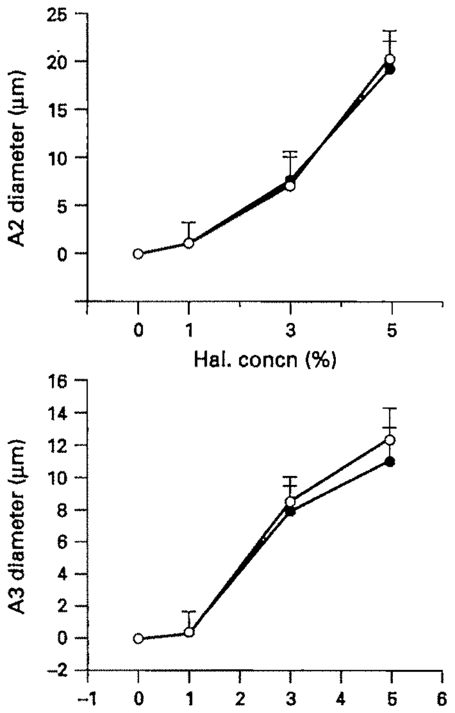

Figure 1 Increase in A2 (top) and A3 (bottom) diameter in response to 0–5 % halothane (Hal.) (mean, SD). First curve (●) = cumulative dose–response curve to administration of halothane (0, 1, 3 and 5 %) performed after a baseline measurement of arteriolar diameter. Second curve (○) = cumulative dose–response curve to administration of halothane performed after a 15-min wash-out period during which the muscle was irrigated with drug-free Krebs' solution. Halothane induced significant dose-dependent A2 and A3 dilatation ($P < 0.0001$) which was not different between the two dose–response curves.

EFFECTS OF HALOTHANE ON DIAPHRAGMATIC ARTERIOLAR DIAMETER

Halothane administered in concentrations of 0–5 % produced dose-dependent dilatation of diaphragmatic A2 and A3 arterioles (factor "dose" $P < 0.0001$ in both arteriolar orders). It must be noted, however, that in both arteriolar orders, dilatation was not observed until 3 % halothane was given (fig. 1).

The effect of halothane was completely reversible. When diaphragmatic muscle surface was washed after administration of halothane, A2 and A3 diameters were not different from baseline values (44.21 (6.50) µm and 25.71 (4.21) µm *vs* 46.12 (5.21) µm and 27.12 (3.85) µm, for A2 and A3, respectively). Furthermore, the dilatator capacity of the arterioles remained intact after halothane, as demonstrated by the similarity between the two dose–response curves to this agent performed with a 15-min washing period interval (fig. 1). Doses of halothane in Krebs' solution at the different concentrations used in this study are presented in table 1.

EFFECTS OF HALOTHANE IN THE PRESENCE OF LNA, MEFENAMIC ACID AND INDOMETHACIN

Baseline arteriolar diameters did not differ between the different groups of animals (table 2). LNA 300 µmol litre^{-1} mefenamic acid 20 µmol litre^{-1} and indomethacin 20 µmol litre^{-1} produced significant reduction in basal diaphragmatic arteriolar diameters (table 2). After LNA superfusion, A2 and A3 diameters were 85 (11) % ($P < 0.001$) and 84 (11) % ($P < 0.001$) of baseline values, respectively. After mefenamic acid superfusion, A2 and A3 diameters were 93 (3) % ($P < 0.001$) and 93 (6) % ($n = 32$; $P < 0.001$) of baseline values, respectively. After indomethacin superfusion, A2 and A3 diameters were 97 (5) % ($P < 0.05$) and 91 (4) % ($P < 0.001$) of baseline values, respectively. The reduction in diameter was related specifically to the inhibitors as superfusion of the diaphragm during a similar period with drug-free Krebs' solution did not result in any significant modification in arteriolar diameters (table 2).

Halothane-induced arteriolar dilatation was not modified by LNA (the interaction between "dose" and "absence or presence of inhibitor" was not significant for A2 and A3, when group C was compared with group LNA) (fig. 2). In contrast, halothane-induced increase in A2 and A3 diameters was almost totally inhibited by mefenamic acid

Table 1 Halothane doses (mg litre^{-1}) in Krebs' solution assessed by chromatography (mean (SD)). Number of samples for each concentration of halothane is seven. Halothane was not detected at a 0 % delivered concentration. The increase in the delivered concentration of halothane resulted in a significant increase in halothane concentration in Krebs' solution

Delivered concn	Dose (mg litre^{-1})
1 %	37.31 (7)
3 %	67.1 (8)
5 %	110.1 (1.2)

Table 2 Arteriolar diameters in the different groups of animals (mean (SD) and [number of arterioles studied]). LNA = $N\omega$-nitro-L-arginine; MA = mefenamic acid; INDO = indomethacin; C = control. No significant differences between the values at baseline. A significant reduction in diameter was observed after administration of LNA, MA and INDO (*$P < 0.05$)

	A2 (μm)		A3 (μm)	
Group	Baseline	After inhibitors	Baseline	After inhibitors
LNA	44.82 (5.91) [9]	38.36 (4.45)*	25.73 (4.98) [12]	21.71 (4.87)*
MA	49.13 (5.26) [10]	45.98 (5.36)*	29.32 (5.76) [12]	26.51 (5.63)*
INDO	44.08 (5.81) [9]	42.78 (5.71)*	24.91 (4.21) [9]	22.81 (3.82)*
C	44.63 (6.96) [9]	44.20 (6.80)	25.71 (6.08) [12]	25.20 (6.10)

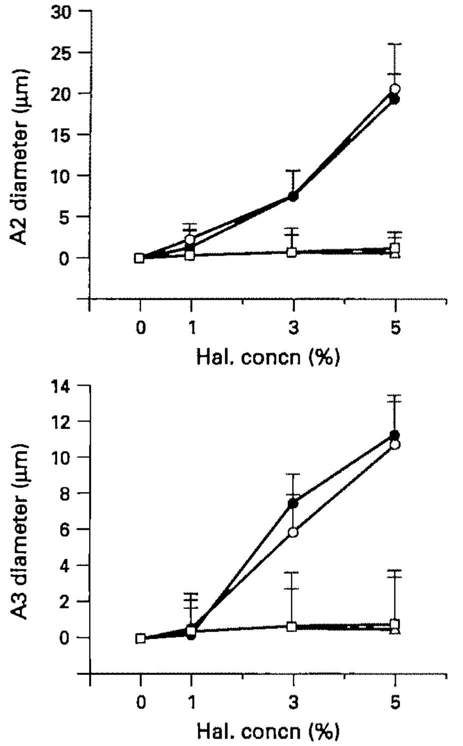

Figure 2 Increase in A2 (top) and A3 arteriole (bottom) diameter in response to 0–5 % halothane (Hal.) in the control group (●) ($n = 9$ and $n = 12$ arterioles for A2 and A3, respectively), group LNA receiving $N\omega$-nitro-L-arginine 300 μmol litre^{-1} (○) ($n = 9$ and $n = 12$ arterioles for A2 and A3, respectively), group MA receiving mefenamic acid 20 μmol litre^{-1} (△) ($n = 10$ and $n = 12$ arterioles for A2 and A3, respectively) and group INDO receiving indomethacin 20 μmol litre^{-1} (□) ($n = 9$ and $n = 9$ arterioles for A2 and A3, respectively) (mean, SD). Halothane induced significant dose-dependent A2 and A3 dilatation ($P < 0.0001$) which was not altered by administration of LNA but reduced significantly by mefanamic acid and indomethacin.

(interaction between factor "dose" and factor "absence or presence of inhibitor", $P < 0.0001$ for each arteriolar order, when group C was compared with group MA). A similar result was observed with indomethacin (interaction between factor "dose" and factor "absence or presence of inhibitor", $P < 0.0001$ for each arteriolar order, when group C was compared with group INDO).

Discussion

The main results of this study are that *in vivo*, topically administered halothane in a concentration range of 0–5 % produced dose-dependent dilatation of rat diaphragmatic arterioles and halothane-induced dilatation of diaphragmatic arterioles was abolished significantly by mefenamic acid and indomethacin, but not by LNA.

In this study, assessment of the role of nitric oxide and prostaglandins on the arteriolar responses of the diaphragm to halothane was performed indirectly using selective inhibitors of both pathways: LNA for nitric oxide and mefenamic acid and indomethacin for prostaglandins. A possible criticism of this design is that these agents may exert effects on diaphragmatic arterioles via mechanisms other than nitric oxide and prostaglandin synthesis inhibition, respectively. However, this is very unlikely. First, a large body of evidence has demonstrated that LNA is a potent and specific inhibitor of nitric oxide synthesis *in vitro* [7, 18] and *in vivo* in different vascular regions [19, 20], including diaphragmatic vessels [10, 21]. Furthermore, we demonstrated in a previous study that topically administered LNA, at the concentration used in this study, effectively blocked nitric oxide-mediated dilatation of diaphragmatic arterioles [10]. Second, we found an inhibitory effect of two structurally different inhibitors of prostaglandin synthesis: mefenamic acid and indomethacin [22]. Thus we are confident that the effects of these agents were related specifically to inhibition of the cyclo-oxygenase pathway.

The concentration of halothane in Krebs' solution perfusing the diaphragm is the determinant of its effect on diaphragmatic arterioles. Therefore, we ensured that the increasing concentrations of halothane resulted in increasing concentrations of this agent in Krebs' solution.

In this study halothane was administered topically, thus avoiding any significant effect of modification of arterial pressure. Consequently, the dilatation induced by this agent can be regarded as a direct relaxant effect on diaphragmatic arterioles. However, it must be noted that dilatation was observed only when halothane concentrations were greater than

1%. This is in line with previous *in vivo* data showing that inhalation of halothane at 0.5–1% failed to produce diaphragmatic A2 and A3 dilatation [4]. Furthermore, this confirms previous results of several *in vitro* studies showing that only halothane concentrations greater than 2% dilated KCl- or phenylephrine-precontracted rat aorta and canine carotid and coronary rings immersed in Krebs' solution [5, 23, 24]. Interestingly, Muldoon and co-workers [5] showed, in a canine femoral ring model, that 2% halothane bubbled in Krebs' solution induced significant contraction of these vessels. Although species differences could explain these controversial results, heterogeneity between the different vessels may also be involved. Absence of vasoconstriction of diaphragmatic arterioles during systemic [4] and topical administration of halothane may be related to the fact that properties of the diaphragmatic vessel may differ significantly from those of peripheral skeletal muscles [10].

Several mechanisms may explain diaphragmatic arteriolar dilatation induced by halothane. For example, it has been reported that halothane has a direct effect on smooth muscle calcium homeostasis and also causes endothelium-dependent relaxation [5]. In this study, we investigated this mechanism by assessing the role of two main vasodilator factors synthesized by the endothelium: nitric oxide and prostaglandins.

The absence of effect of LNA on halothane-induced A2 and A3 dilatation suggests that nitric oxide was not involved in the diaphragmatic arteriolar effects of halothane. In contrast, mefenamic acid and indomethacin induced complete inhibition of halothane-induced diaphragmatic arteriolar dilatation. As both agents increased arteriolar tone, suppression of halothane-induced dilatation may be related to this increase in smooth muscle vascular tone, which in turn may attenuate the relaxant effect of halothane. However, this possibility can be excluded as LNA, which induced a greater increase in arteriolar tone than mefenamic acid and indomethacin, did not modify the dilatation caused by halothane. In addition, complete inhibition of halothane-induced diaphragmatic A2 and A3 arteriolar dilatation by mefenamic acid and indomethacin demonstrated that the diaphragmatic arteriolar effect of halothane was mediated exclusively by prostaglandins. This result is in agreement with that reported by Stone and Johns [23] who showed that indomethacin attenuated the decrease in aortic ring tension observed with increasing doses of halothane. However, other effects of halothane, such as development of pulmonary vasoconstriction in dogs, are not mediated by prostaglandins [25]. It is interesting to note that prostaglandins contribute, together with nitric oxide, to modulation of diaphragmatic arteriolar tone [10], a phenomenon which has not been shown in other skeletal muscle microvessels [11, 12]. Thus it is possible to speculate that modulation of the prostaglandins pathway could be an important mechanism of action of pharmacological agents, such as halothane, in affecting the diaphragmatic microcirculation.

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References

1. Vatner S, Smith N. Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. *Circulation Research* 1974; **34**: 155–167.
2. Miller E, Kistner J, Epstein R. Whole-body distribution of radioactivity labelled microspheres in the rat during anesthesia with halothane, enflurane, or ketamine. *Anesthesiology* 1980; **52**: 296–302.
3. Seyde W, Longnecker D. Anesthetic influences on regional hemodynamics in normal and hemorrhaged rats. *Anesthesiology* 1984; **61**: 686–698.
4. Leon A, Boczkowski J, Dureuil B, Vicaut E, Aubier M, Desmonts J. Diaphragmatic microcirculation during halothane and isoflurane exposure in pentobarbital-anesthetized rats. *Journal of Applied Physiology* 1992; 73: 1–4.
5. Muldoon S, Hart J, Bowen K, Freas W. Attenuation of endothelium-mediated vasodilation by halothane. *Anesthesiology* 1988; **68**: 31–37.
6. Jensen N, Todd M, Kramer D, Leonard P, Warner D. A comparison of the vasodilating effects of halothane and isoflurane on the isolated rabbit basilar artery with and without intact endothelium. *Anesthesiology* 1992; **16**: 624–634.
7. Ishii K, Chang B, Kerwin J, Huang Z, Murad F. Nω-nitro-L-arginine: a potent inhibitor of endothelium-derived relaxing factor formation. *European Journal of Pharmacology* 1990; **176**: 219–223.
8. Gross S, Steuhr D, Aisaka E, Jaffe A, Levi R, Griffith O. Macrophage and endothelial cell nitric oxide synthesis: cell type selective inhibition by NG-aminoarginine, NG-nitroarginine and NG-methylarginine. *Biochemical and Biophysical Research Communications* 1990; **170**: 96–103.
9. Flower R. Drugs which inhibit prostaglandin biosynthesis. *Archives of Pharmacology* 1977; **297**: 85–88.
10. Boczkowski J, Vicaut E, Danialou G, Aubier M. Role of nitric oxide and prostaglandins on diaphragmatic arteriolar response to acetylcholine in rats. *Journal of Applied Physiology* 1994; **77**: 590–596.
11. Kaley G, Koller A, Rodenburg J, Messina E, Wolin M. Regulation of arteriolar tone and responses via L-arginine pathway in skeletal muscle. *American Journal of Physiology* 1992; **262**: H987–H992.
12. Nakamura T, Prewitt R. Effect of NG-monomethyl L-arginine on endothelium-dependent relaxation in arterioles of one-kidney, one clip hypertensive rats. *Hypertension* 1991; **17**: 875–880.
13. Boczkowski J, Vicaut E, Aubier M. A model for *in vivo* study of the diaphragmatique microcirculation in the rat. *Microvascular Research* 1990; **40**: 157–167.
14. Intaglietta M, Tompkins W. Microvascular measurements by video image shearing and splitting. *Circulation Research* 1973; **5**: 309–312.
15. Zweifach B, Lipowski H. Pressure-flow relations in blood and lymph microcirculation. In: Renkin E, Michels CC, eds. *Handbook of Physiology*, vol. IV: *The Cardiovascular System*. Bethesda, MD: American Physiology Society, 1984; 252–305.
16. Brachet-Liermain A, Ferrus L, Caroff J. Electron capture detection and measurement of fluothane in blood. *Journal of Chromatography Sciences* 1971; **9**: 49–53.
17. Winer B. *Statistical Principles in Experimental Design*. New York: McGraw-Hill, 1971.
18. Moore P, Al-Swayeh A, Chong N, Evans R, Gibson A. L-N^G-nitro-L-arginine (L-NOARG), a novel L-arginine reversible inhibitor of endothelium-dependent vasodilation in vitro. *British Journal of Pharmacology* 1990; **99**: 408–412.
19. Benyo Z, Kiss G, Szabo C, Czaki C, Kovach A. Importance of basal nitric oxide synthesis in regulation of myocardial blood flow. *Cardiovascular Research* 1992; **25**: 700–703.
20. Mügge A, Lopez A, Piegors D, Breese K, Heistad D.

Acetylcholine-induced vasodilatation in rabbit hindlimb in vivo is not inhibited by analogues of L-arginine. *American Journal of Physiology* 1991; **260**: H242–H247:

21. Hussain S, Stewart D, Ludemann J, Magder S. Role of endothelium-derived relaxing factor in active hyperemia on the canine diaphragm. *Journal of Applied Physiology* 1992; **72**: 2393–2401.
22. Flower R, Vane J. Inhibition of prostaglandin biosynthesis. *Biochemical Pharmacology* 1974; **23**: 1439–1450.
23. Stone D, Johns R. Endothelium-dependent effects of halothane, enflurane, and isoflurane on isolated rat aortic vascular rings. *Anesthesiology* 1989; **71**: 126–132.
24. Hatano Y, Nakamura K, Yakushiji T, Nishiwada M, Mori K. Comparison of the direct effects of halothane and isoflurane on large and small coronary arteries isolated from dogs. *Anesthesiology* 1990; **73**: 513–517.
25. Chen B, Nyhan D, Fehr D, Goll H, Murray P. Halothane anesthesia causes active flow-independent pulmonary vasoconstriction. *American Journal of Physiology* 1990; **259**: H74–H83.

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Ketamine inhibits nitric oxide production in mouse-activated macrophage-like cells

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Summary

We have investigated the effects of ketamine on nitric oxide produced by activated macrophages using a murine macrophage-like cell line, J774. Cells were incubated for 18 h under stimulation with lipopolysaccharide and interferon-γ or lipoteichoic acid and interferon-γ, with various concentrations of ketamine (6–600 μmol litre^{-1}). Nitric oxide production was assessed by measuring nitrite, a stable by-product of nitric oxide breakdown, in the medium. Other *N*-methyl-D-aspartate receptor antagonists, MK-801 (150 μmol litre^{-1}) and dextromethorphan (150 μmol litre^{-1}) were also tested. In addition, we studied the effects of ketamine on production of tumour necrosis factor-α by activated macrophages. Ketamine inhibited nitrite production dose-dependently with both lipopolysaccharide- and lipoteichoic acid-activated macrophages by up to approximately 65% at the highest ketamine concentration (600 μmol litre^{-1}). Neither MK-801 nor dextromethorphan had an inhibitory effect. Ketamine also suppressed production of tumour necrosis factor-α. The data show that ketamine inhibited nitric oxide production by activated macrophages probably, in part, via inhibition of production of tumour necrosis factor-α, an autocrine stimulatory factor for nitric oxide production, but not via the NMDA receptor pathway, which is involved in neuronal nitric oxide production. (*Br. J. Anaesth.* 1996; **77**: 238–242)

Key words

Anaesthetics i.v., ketamine. Pharmacology, nitric oxide. Polypeptides, cytokines. Mouse. Model, mouse. Immune response.

Nitric oxide is a short-lived radical produced by enzymatic oxidation of L-arginine. At least two distinct forms of nitric oxide synthase have been reported; constitutive and inducible [1, 2]. Constitutive nitric oxide synthase is distributed in the vascular endothelium and in the brain [1, 2]. Nitric oxide produced by constitutive nitric oxide synthase in the endothelium acts as a vasodilator and nitric oxide produced by constitutive nitric oxide synthase in the brain acts as a neurotransmitter. Inducible nitric oxide synthase is found in activated macrophages and in various types of cells. Activated macrophages produce large amounts of nitric oxide, which is considered an essential mediator in host defence because of its cytotoxic effects on tumour cells and micro-organisms [1, 2]. The cytotoxic effect of nitric oxide derived from activated macrophages is so strong that not only target cells but also normal surrounding cells may be damaged. Recent investigations have shown that nitric oxide from activated macrophages is involved in the pathogenesis of various types of diseases, such as septic shock [3], diabetes mellitus [4], reperfusion injury [5] and ischaemic neuronal damage [6]. In ischaemic neuronal damage, glutamate is thought to play a pivotal role via the subsequent activation of *N*-methyl-D-aspartate (NMDA) receptors [7]. Recently, not only glutamate but also nitric oxide produced by the brain macrophage, microglia, has been reported to be involved in the pathogenesis of neuronal damage [8]. Ketamine, a dissociative general anaesthetic, blocks excitation involving NMDA receptors and acts as a noncompetitive NMDA receptor antagonist. Ketamine and other NMDA receptor antagonists have been shown to reduce ischaemia- or NMDA-induced neuronal damage [9, 10]. Evidence has subsequently appeared suggesting that MK-801, a NMDA receptor antagonist, and ketamine, inhibit nitric oxide produced by constitutive nitric oxide synthase in cultured cerebral neurones [11].

In this study we have investigated the effect of ketamine on nitric oxide production from inducible nitric oxide synthase in activated macrophages and speculate on the possibility of ketamine offering protection against nitric oxide-mediated tissue injury, such as neurotoxicity in hypoxic cerebral damage and microvascular injury in septic shock.

Materials and methods

CHEMICALS

Chemicals used in this study were obtained from the following sources: ketamine hydrochloride, lipopolysaccharide, lipoteichoic acid, mouse interferon-γ,

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dextromethorphan, dexamethasone and fetal calf serum (FCS) from Sigma (St Louis, MO, USA); MK-801 from Research Biochemicals International (Natick, MA, USA); RPMI 1640 medium containing kanamycin 50 µg ml^{-1} from the Research Foundation for Microbial Diseases of Osaka University (Osaka, Japan); sulphanilamide, naphthylethylene diamine dihydrochloride, H_3PO_4, $NaNO_2$ from Wako Pure Chemical Industries, Ltd (Osaka, Japan).

CELL CULTURE

The mouse macrophage-like cell line, J774, derived from the tumour of a female BALB/c mouse, has been shown to possess characteristics typical of macrophages, including phagocytic properties and the ability to produce pro-inflammatory cytokines and nitric oxide [12]. This cell line was kindly provided by the Japanese Cancer Research Resources Bank. J774 cells were maintained in RPMI 1640 medium supplemented with 10 % fetal calf serum and kanamycin 50 µg ml^{-1} at 37 °C in an atmosphere of 5 % carbon dioxide. Cells were plated in 48-well culture plates at a density of 10^6 ml^{-1} and allowed to adhere for 2 h; the medium was then replaced with fresh medium containing varying amounts of reagents. After 18 h of incubation, supernatants were harvested to determine nitrite, tumour necrosis factor-α and lactate dehydrogenase release and the cells were subjected to viability assay using trypan blue.

NITRITE MEASUREMENT

The amount of nitric oxide released during incubation was determined by measuring nitrite, a stable by-product of nitric oxide breakdown. Nitrite measurement is widely accepted as a means of evaluating nitric oxide production indirectly *in vitro* [13–15] and *in vivo* [16, 17]. Nitrite in culture supernatant was assayed by Griess reaction, as described previously [18]. Briefly, 100 µl of medium was incubated with 100 µl of Griess reagent (1 % sulphanilamide, 0.1 % naphthylethylene diamine dihydrochloride and 2 % H_3PO_4) for 10 min at room temperature, and then the absorbance at 550 nm was measured. Nitrogen dioxide concentration was determined using $NaNO_2$ as a standard.

TNF ASSAY

Secretion of tumour necrosis factor-α was determined by enzyme-linked immunosorbent assay (ELISA) using a mouse tumour necrosis factor-α ELISA kit (Endogen, Inc., Cambridge, MA, USA).

CELL VIABILITY

To confirm that ketamine in the concentrations used in this study had no cytotoxic effect on J774 cells, cell viability was determined both by trypan blue exclusion assay and by measuring the amount of lactate dehydrogenase released into the medium, a well-characterized indicator of toxicity, with a commercial kit (lactate dehydrogenase cytotoxicity test; Wako Pure Chemical Industries Ltd, Osaka, Japan). Cell viability was assessed by comparing the percentage of cells which were not stained by trypan blue with PBS-treated cells (a negative control); lactate dehydrogenase release was expressed as a percentage of the total amount of lactate dehydrogenase present in the cells, which was determined by measuring Triton X-treated cell lysate.

Cell viability determined by trypan blue staining was more than 95 % in all groups. Ketamine, even at the highest concentration used in this study (600 µmol litre^{-1}), did not release lactate dehydrogenase; ketamine 600-µmol litre^{-1} samples released 18.3 (0.2) % and control samples released 18.3 (0.6) % of total lactate dehydrogenase (Triton-X lysate).

DATA ANALYSIS

All values were derived from more than three independent experiments. Data were expressed as mean (SEM) and differences between values were analysed using the Mann–Whitney *U* test or ANOVA; when $P < 0.05$, differences were considered significant.

Results

NITRITE PRODUCTION BY MACROPHAGES ACTIVATED BY LIPOPOLYSACCHARIDE AND INTERFERON-γ OR LIPOTEICHOIC ACID AND INTERFERON-γ

Both lipoteichoic acid, a component of the cell walls of gram-positive bacteria, and lipopolysaccharide, which is part of the cell walls of gram-negative bacteria, are known to induce macrophages to produce nitric oxide [19]. Interferon-γ enhances this nitric oxide production. As shown in table 1, lipopolysaccharide 10 ng ml^{-1} or lipoteichoic acid 5 µg ml^{-1} induced nitrite production by macrophages, when treated with interferon-γ 100 u. ml^{-1}.

EFFECTS OF KETAMINE ON NITRITE PRODUCTION BY MACROPHAGES

Various concentrations of ketamine (6–600 µmol litre^{-1}) were added to the macrophage culture samples concurrently with lipopolysaccharide or lipoteichoic acid stimuli. As shown in figure 1, ketamine suppressed nitric oxide production dose-dependently, evaluated as nitrite accumulation, at concentrations of 30–600 µmol litre^{-1} in macrophages activated by lipopolysaccharide and interferon-γ at concentration of 15–600 µmol litre^{-1} in samples activated by lipoteichoic acid and interferon-γ. The IC_{50} for lipopolysaccharide- and

Table 1 Nitrite production by activated macrophages (mean (SEM)). J774 cells were incubated with various types of stimuli for 18 h and the amount of nitrite production was determined by Griess reaction. LPS = Lipopolysaccharide, IFNγ = interferon-γ and LTA = lipoteichoic acid

Stimulus	Nitrite (µmol litre^{-1})
LPS (10 ng ml^{-1})+IFNγ (100 u. ml^{-1})	37.9 (0.8)
LTA (5 µg ml^{-1})+IFNγ (100 u. ml^{-1})	42.7 (1.1)
None	0.4 (0.1)

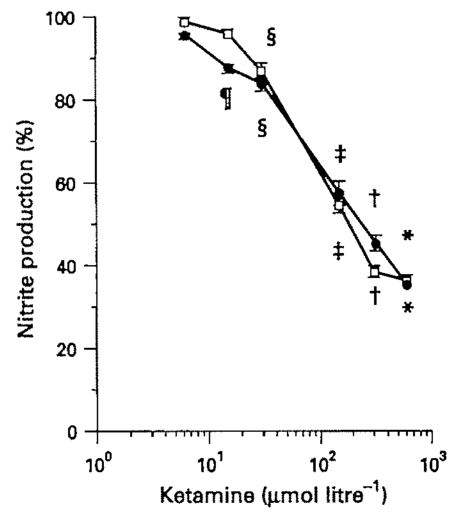

Figure 1 Inhibition by ketamine of nitrite production by macrophages activated by lipopolysaccharide 10 ng ml^{-1} and interferon-γ 100 u. ml^{-1} (□) or lipoteichoic acid 5 µg ml^{-1} and interferon-γ 100 u. ml^{-1} (●). J774 cells were incubated for 18 h under stimulation with lipopolysaccharide and interferon-γ or lipoteichoic acid and interferon-γ, with various amounts of ketamine (6–600 µmol $litre^{-1}$). Nitric oxide production was determined by measuring nitrite in the medium. Values are expressed as mean (SEM) percentage of control (containing no ketamine). Ketamine inhibited nitric oxide production by macrophages dose-dependently. The IC_{50} values for lipopolysaccharide- and interferon-γ- and lipoteichoic acid- and interferon-γ-induced nitric oxide production by macrophages were 281 and 266 µmol $litre^{-1}$, respectively. $*P < 0.05$ *vs* 300, 150, 60, 30, 6 and 0 µmol $litre^{-1}$; $\dagger P < 0.05$ *vs* 150, 60, 30, 6 and 0 µmol $litre^{-1}$; $\ddagger P < 0.05$ *vs* 60, 30, 6 and 0 µmol $litre^{-1}$; $\S P < 0.05$ *vs* 30, 6 and 0 µmol $litre^{-1}$; $\P P < 0.05$ *vs* 6 and 0 µmol $litre^{-1}$.

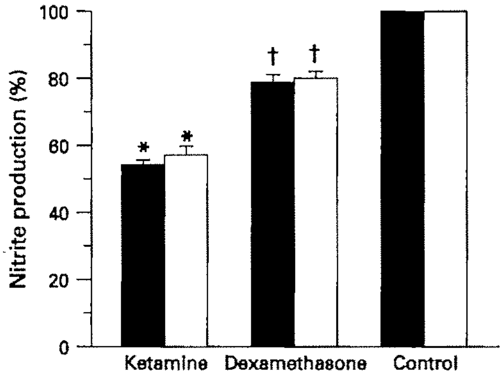

Figure 2 Comparison of the effects of ketamine 150 µmol $litre^{-1}$ and dexamethasone 150 µmol $litre^{-1}$, a well-known inhibitor of inducible nitric oxide synthase induction, on nitrite production by macrophages activated by lipopolysaccharide 10 ng ml^{-1} and interferon-γ 100 u. ml^{-1} (■) or lipoteichoic acid 5 µg ml^{-1} and interferon−γ 100 u. ml^{-1} (□). The inhibitory effect of ketamine was stronger than that of dexamethasone at the same concentration. Values are expressed as mean (SEM) percentages of control (stimuli only). $*P < 0.05$ *vs* dexamethasone and control; $\dagger P < 0.05$ *vs* control.

interferon-γ-induced nitrite production by macrophages was 281 µmol $litre^{-1}$, and 266 µmol $litre^{-1}$ for lipoteichoic acid- and interferon-γ-induced nitrite production. The extent of inhibition of nitrite production by ketamine 150 µmol $litre^{-1}$ was stronger than that of dexamethasone 150 µmol $litre^{-1}$, which is a well-known inhibitor of nitric oxide production by activated macrophages [20] (fig. 2).

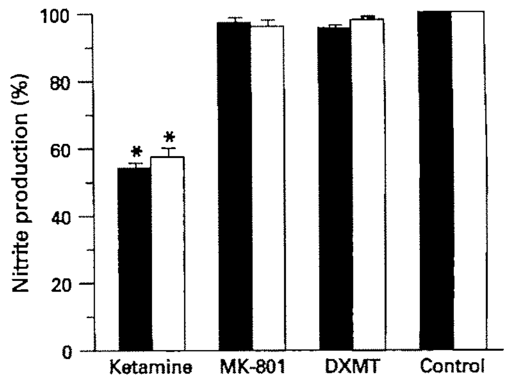

Figure 3 Comparison of the effects of ketamine 150 µmol $litre^{-1}$ and other NMDA receptor antagonists on nitrite production by macrophages activated by lipopolysaccharide 10 ng ml^{-1} and interferon-γ 100 u. ml^{-1} (■) or lipoteichoic acid 5 µg ml^{-1} and interferon-γ 100 u. ml^{-1} (□). MK-801 150 µmol $litre^{-1}$ and dextrometrophan (DXMT) 150 µmol $litre^{-1}$, both potent NMDA receptor antagonists, failed to inhibit nitric oxide production. Values are expressed as mean (SEM) percentages of control (stimuli only). $*P < 0.05$ *vs* control.

EFFECTS OF OTHER NON-COMPETITIVE NMDA RECEPTOR ANTAGONISTS ON NITRITE PRODUCTION BY ACTIVATED MACROPHAGES

In order to investigate if NMDA receptor pathways are involved in the inhibitory effect of ketamine on nitrite production, we tested the effects of two potent non-competitive NMDA receptor antagonists, MK-801 and dextromethorphan. In contrast with ketamine, neither MK-801 150 µmol $litre^{-1}$ nor dextromethorphan 150 µmol $litre^{-1}$ inhibited nitrite production in lipopolysaccharide- and lipoteichoic acid-activated macrophages (fig. 3). Similar doses of these antagonists have been reported to be adequate to block the NMDA receptor channels of neuronal cells [11, 21, 22].

EFFECTS OF KETAMINE ON TNF PRODUCTION BY ACTIVATED MACROPHAGES

Tumour necrosis factor-α is a pro-inflammatory cytokine released from activated macrophages and a key mediator in septic shock [23]. Because the endogenous production of tumour necrosis factor-α has been reported to stimulate nitric oxide production in the autocrine system [24], we examined the effects of ketamine on production of tumour necrosis factor-α.

As shown in table 2, ketamine suppressed production of tumour necrosis factor-α by lipopolysaccharide- and lipoteichoic acid-activated macrophages dose-dependently.

Discussion

Although the extent of influence of anaesthetics on host defence and the immune system is largely unknown, some of the immunosuppressive effects of anaesthetic agents *in vitro* have been reported [25, 26]. Under normal conditions, the immune system provides essential protection for the host, but if the immune system is overactivated or improperly activated, it becomes excessively cytotoxic and can

Table 2 Inhibition by ketamine of tumour necrosis factor-α (TNF-α) production from macrophages activated by lipopolysaccharide (LPS) and interferon-γ (IFNγ) or lipoteichoic acid (LTA) and IFNγ. J774 cells were incubated for 18 h under stimulation with LPS and IFNγ or LTA and IFNγ with various amount of ketamine. The amount of TNF-α production was determined by ELISA. Values are expressed as mean (SEM) percentages of control (no ketamine, stimuli only). $^*P < 0.05$ *vs* control; $^\dagger P < 0.05$ *vs* 10 $\mu g\ ml^{-1}$ and control

Concentration of ketamine ($\mu mol\ litre^{-1}$)	% Production of TNF-α	
	LPS (10 $ng\ ml^{-1}$) + IFNγ (100 u. ml^{-1})	LTA (5 $\mu g\ ml^{-1}$) + IFNγ (100 u. ml^{-1})
0	100	100
30	83.5 (7.9)*	81.8 (4.1)*
300	17.0 (1.0)†	35.4 (4.1)†

damage normal tissues, typically seen in sepsis [27], ARDS [28], autoimmune diseases [29] and ischaemic brain injury [30]. In this regard, further investigation of the immunosuppressive effects of anaesthetic agents may lead to new strategies in treating disorders related to overactivation of the immune system. Nitric oxide is implicated in the injury of tissues in various organs [1, 2]; in this study we focused on nitric oxide produced by inducible nitric oxide synthase in activated macrophages, and showed that ketamine inhibited nitric oxide production dose-dependently.

Recently the role of nitric oxide endogenously generated by inducible nitric oxide synthase in the physiology and pathophysiology of organs has been better appreciated and the mechanisms which may regulate nitric oxide production have been investigated. The list of factors shown to inhibit nitric oxide production continues to grow: corticosteroid [19], transforming growth factor-β [13], interleukin-4 [14], interleukin-10 [24], macrophage deactivating factor [31] and macrophage-stimulating protein [15] have been reported to inhibit the induction of nitric oxide production by macrophages stimulated by lipopolysaccharide or cytokines. We found the inhibitory effect of ketamine 150 $\mu mol\ litre^{-1}$ was stronger than that of dexamethasone 150 $\mu mol\ litre^{-1}$. Because we still do not know how ketamine inhibits nitric oxide production by macrophages, we also examined the involvement of NMDA receptors. Activation of NMDA receptors in the central nerve system results in nitric oxide synthesis by constitutive nitric oxide synthase in neuronal cells [32]. Another study showed that ketamine and other non-competitive NMDA receptor antagonists inhibited nitric oxide production in cultured cerebral neurones [11].

Although an NMDA receptor has yet to be identified in macrophages, we tested the effects of MK-801 and dextromethorphan on the production of nitric oxide by activated macrophages and found no inhibition. These results indicate that whether or not macrophages possess NMDA receptors, involvement of NMDA receptors in the inhibition of nitric oxide production by ketamine would still seem unlikely.

Ketamine inhibited production of tumour necrosis factor-α dose-dependently, a finding consistent with a previous report [26]. This suggests that inhibition of nitric oxide production by ketamine may be caused partially by inhibition of endogenous production of tumour necrosis factor-α.

The presence of activated macrophages at sites of neurone damage, observed in brain injury and degenerative brain, has lead to the suggestion that the cytotoxicity of macrophages is responsible for the damage [33]. Recent experiments have provided further evidence that macrophages are responsible for neuronal damage; reduction in the recruitment of macrophages, achieved by body irradiation or by macrophage inactivation with colchicine, which inhibits the assembly of microtubules and suppresses the phagocytic and secretory functions, reduces cell death in ischaemic injury or ibotenic acid-induced brain damage [30, 34]. Nitric oxide released by activated macrophages has also been found to be cytotoxic to neurones [10]. The ability of ketamine to act against neuronal damage may thus be expected not only to derive from inhibition of the NMDA receptor in neurones [35, 36] but also partially from inhibition of nitric oxide production by macrophages in the brain.

In septic shock, or systemic inflammatory response syndrome (SIRS), tumour necrosis factor-α released from macrophages plays a pivotal role in pathogenesis [23]. Tumour necrosis factor-α alone, however, cannot explain the complex pathophysiological alternation in SIRS. There has been speculation concerning the participation of alternative mediators, including other cytokines and nitric oxide [37]. In this context, ketamine may prove worthy of consideration in a new form of therapy because, *in vitro*, it inhibits both tumour necrosis factor-α and nitric oxide production by macrophages. Reported serum concentration of ketamine used in anaesthetic doses, however, are less than 80 $\mu mol\ litre^{-1}$ in animals [38, 39] and less than 7 $\mu mol\ litre^{-1}$ in humans [40, 41]. The latter is small compared with the effective values in this study. If higher doses of ketamine were administered, the inhibitory effects found in this study may be clinically significant. Further investigation is needed to determine the possible therapeutic uses of ketamine.

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References

1. Nathan C. Nitric oxide as a secretory product of mammalian cells. *FASEB Journal* 1992; 6: 3051–3064.
2. Nussler AK, Billar TR. Inflammation, immunoregulation, and inducible nitric oxide synthase. *Journal of Leukocyte Biology* 1993; 54: 171–178.
3. Ochoa JB, Udekwu AO, Billar TR, Curran RD, Cerra FB, Simmons RL, Peitzman AB. Nitrogen oxide levels in patients after trauma and sepsis. *Annals of Surgery* 1991; 214: 621–626.
4. Corbett JA, Wang JL, Hughes JH, Wolf BA, Sweetland MA, Lancaster JR jr, McDaniel ML. Nitric oxide and cGMP formation induced by interleukin-1β in Islets of Langerhans: evidence for an effector role of nitric oxide in islet dysfunction. *Biochemical Journal* 1992; 287: 229–235.

5. Seekamp A, Mulligan MS, Till GO, Ward PA. Requirements for neutrophil products and L-arginine in ischemia–reperfusion injury. *American Journal of Pathology* 1993; **142**: 1217–1226.
6. Fabian RH, Rea HC. Neuronal toxicity by macrophages in mixed brain cell culture is augmented by antineuronal IgG and dependent upon nitric oxide synthesis. *Journal of Neuroimmunology* 1993; **44**: 95–102.
7. Beal MF. Mechanisms of exitotoxicity in neurologic diseases. *FASEB Journal* 1992; **6**: 3338–3344.
8. Peterson PK, Hu S, Anderson R, Chao CC. Nitric oxide production and neurotoxicity mediated by activated microglia from human versus mouse brain. *Journal of Infectious Diseases* 1994; **170**: 457–460.
9. Rothman SM, Thurston JH, Hauhart RE, Clark GD, Solomon JS. Ketamine protects hippocampal neurons from anoxia in vitro. *Neuroscience* 1987; **21**: 673–678.
10. Chan PK, Chu L. Ketamine protects cultured astrocytes from glutamate-induced swelling. *Brain Research* 1989; **487**: 380–383.
11. Gonzales JM, Loeb AL, Reichard PS, Steven IBS. Ketamine inhibits glutamate-, *N*-methyl-D-aspartate, and quisqualate-stimulated cGMP production in cultured cerebral neurons. *Anesthesiology* 1995; **82**: 205–213.
12. Fujihara M, Ito N, Pace JL, Watanabe Y, Russell SW, Suzuki T. Role of endogenous interferon-β in lipopolysaccharide-triggered activation of the inducible nitric oxide. synthase gene in a mouse macrophage cell line, J774. *Journal of Biological Chemistry* 1994; **269**: 12773–12778.
13. Vodovotz Y, Bogdan C, Paik J, Xie QW, Nathan C. Mechanisms of suppression of macrophage nitric oxide release by transforming growth factor β. *Journal of Experimental Medicine* 1993; **178**: 605–613.
14. Cenci E, Romani L, Mencacci A, Spaccapelo R, Schiaffella E, Puccetti P, Bistoni F. Interleukin-4 and interleukin-10 inhibit nitric oxide-dependent macrophage killing of *Candida albicans*. *European Journal of Immunology* 1993; **23**: 1034–1038.
15. Wang MH, Cox GW, Yoshimura T, Sheffler LA, Skeel A, Leonard EJ. Macrophage-stimulating protein inhibits induction of nitric oxide production by endotoxin- or cytokine-stimulated mouse macrophages. *Journal of Biological Chemistry* 1994; **269**: 14027–14031.
16. Drobyski WR, Keever CA, Hanson GA, McAuliffe T, Griffith OW. Inhibition of nitric oxide production is associated with enhanced weight loss, decreased survival, and impaired alloengraftment in mice undergoing graft-versus-host disease after bone marrow transplantation. *Blood* 1994; **84**: 2363–2373.
17. Florquin S, Amraoui Z, Dubois C, Decuypre J, Goldman M. The protective role of endogenously synthesized nitric oxide in staphylococcal enterotoxin B-induced shock in mice. *Journal of Experimental Medicine* 1994; **180**: 1153–1158.
18. Stuehr DJ, Nathan CE. Nitric oxide: a macrophage product responsible for cytostasis and respiratory inhibition in tumor target cells. *Journal of Experimental Medicine* 1989; **169**: 1543–1555.
19. Cunha FQ, Moss DW, Leal LMCC, Moncada S, Liew FY. Induction of macrophage parasiticidal activity by *Staphylococcus aureus* and exotoxins through the nitric oxide synthesis pathway. *Immunology* 1993; **78**: 563–567.
20. Moncada S, Palmar RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacological Reviews* 1991; **43**: 109–115.
21. Huang JC, Salt TE, Voaden MJ, Marshall J. Non-competitive NMDA-receptor antagonists and anoxic degeneration of the ERG B-wave *in vitro*. *Eye* 1991; **5**: 476–480.
22. Trube G, Netzer R. Dextromethorphan: cellular effects reducing neuronal hyperactivity. *Epilepsia* 1994; 35 (Suppl.): S62–S67.
23. Mathison JC, Wolfson E, Ulevitch RJ. Participation of tumor necrosis factor in the mediation of gram negative bacterial lipopolysaccharide-induced injury in rabbits. *Journal of Clinical Investigation* 1988; **81**: 1925–1937.
24. Oswald IP, Wynn T, Sher A, James SL. Interleukin 10 inhibits macrophage microbicidal activity by blocking the endogenous production of tumor necrosis factor α required as a costimulatory factor for interferon γ-induced activation. *Proceedings of the National Academy of Sciences USA* 1992; **89**: 8676–8680.
25. Krumholz W, Hempelmann G. Propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Esherichia coli* by polymorphonuclear leucocytes in vitro. *Canadian Journal of Anaesthesia* 1994; **41**: 446–449.
26. Takenaka I, Ogata M, Koga K, Matsumoto T, Shigematsu A. Ketamine suppresses endotoxin-induced tumor necrosis factor alpha production in mice. *Anesthesiology* 1994; **80**: 402–408.
27. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s. Systemic inflammatory responses and organ dysfunction. *Journal of the American Medical Association* 1994; **271**: 226–233.
28. Rinaldo JE, Rogers RM. Adult respiratory distress syndrome, changing concepts of lung injury and repair. *New England Journal of Medicine* 1982; **206**: 900–909.
29. Weiss SJ. Tissue destruction by neutrophil. *New England Journal of Medicine* 1989; **320**: 365–376.
30. Guilan D, Robertson C. Inhibition of mononuclear phagocytes reduces ischemic injury in the spinal cord. *Annals of Neurology* 1990; **27**: 33–42.
31. Ding A, Nathan CF, Graycar J, Derynck R, Stuehr DJ, Srimal S. Macrophage deactivating factor and transforming growth factor-β1, -β2, -β2 inhibit induction of macrophage nitrogen oxide syntheses by IFN-γ. *Journal of Immunology* 1990; **145**: 940–944.
32. Garthwaite J, Charles SL, Chess-Williams R. Endothelium-derived relaxing factor release on activation of NMDA receptor suggests role as intercellular messenger in the brain. *Nature* (*London*) 1988; **336**: 385–388.
33. Piani D, Spranger M, Frei K, Schaffner, A, Fontana A. Macrophage-induced cytotoxicity of *N*-methyl-D-aspartate receptor positive neurones involves excitatory amino acid rather than reactive oxygen intermediates and cytokines. *European Journal of Immunology* 1992; **22**: 2429–2436.
34. Coffey PJ, Perry VH, Rawlins JNP. An investigation into the early stages of the inflammatory response following ibotenic acid-induced neuronal degeneration. *Neuroscience* 1990; **35**: 121–132.
35. Church J, Zeman S, Lodge D. The neuroprotective action of ketamine and MK-801 after transient cerebral ischemia in rats. *Anesthesiology* 1988; **69**: 702–709.
36. Marcoux FW, Goodrich JE, Dominick MA. Ketamine prevents ischemic neuronal injury. *Brain Research* 1988; **452**: 329–335.
37. Corradin SB, Heumann D, Gallay P, Smith J, Mauel J, Glauser MP. Bactericidal/permeability-increasing protein inhibits induction of macrophage nitric oxide production by lipopolysaccharide. *Journal of Infectious Diseases* 1994; **169**: 105–111.
38. Muri WW, Sams R. Effects of ketamine infusion on halothane minimal alveolar concentration in horse. *American Journal of Veterinary Research* 1992; **53**: 1802–1806.
39. Schwieger IM, Szlam F, Hug CC jr. The pharmacokinetics of ketamine in dogs anesthetized with enflurane. *Journal of Pharmacokinetics and Biopharmacology* 1991; **19**: 145–156.
40. Hartvig P, Larsson E, Joachimmsson PO. Postoperative analgesia and sedation following pediatric cardiac surgery using a constant infusion of ketamine. *Journal of Cardiothoracic and Vascular Anesthesia* 1993; **7**: 148–153.
41. Chang T, Glazko AJ. A gas chromatographic assay for ketamine in human plasma. *Anesthesiology* 1972; **36**: 401–404.

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Potentiation of local lignocaine-induced sensory block by calcium channel blockers in rats

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Summary

We have studied the effects of three different types of calcium channel blockers (verapamil, diltiazem, and nicardipine) on local lignocaine sensory block. The standardized tail flick test was used to measure the duration and degree of lignocaine-induced conduction block in rats. After obtaining baseline tail flick latencies (mean 3.2 s), two 100-µl doses of 0.3% lignocaine alone, a combination of verapamil 25, 100 or 200 µg, diltiazem 25, 100 or 200 µg, or nicardipine 0.5, 1.0 or 2.0 µg, and a large dose of calcium channel blockers (verapamil 200 µg, diltiazem 200 µg or nicardipine 2.0 µg) were injected on opposite sites of the tail base and the tail flick test was performed every 5 min for 45 min. A large dose of the calcium channel blockers showed no prolongation of tail flick latencies. Administration of 0.3% lignocaine alone produced a significant increase in tail flick thresholds and the peak effect of the percentage maximum possible effect (%MPE) was demonstrated at 5 min after drug injection (mean %MPE 28.8%; $P < 0.01$ *vs* baseline). Co-administration of 0.3% lignocaine and three doses of verapamil produced significant increases in area under the curve (AUC) in a dose-dependent fashion. Mean AUC values for 0.3% lignocaine alone and a combination of verapamil 25, 100 or 200 µg were 217.5, 502.5, 529.1 and 1600.3, respectively. Almost similar patterns of augmentation in AUC values were demonstrated after addition of different doses of diltiazem or nicardipine to 0.3% lignocaine. We conclude that the use of mixtures of local anaesthetic and calcium channel blocker potentiated lignocaine sensory block at the level of the peripheral nerves. (*Br. J. Anaesth.* 1996; **77**: 243–247).

Key words

Anaesthetics local, lignocaine. Calcium channel block, verapamil. Calcium channel block, diltiazem. Calcium channel block, nicardipine. Rat.

The primary action of local anaesthetics reversibly blocks conduction of nerve impulses by preventing increases in the permeability of the nerve membrane to sodium ions. Calcium movement is essential for normal sensory processing and plays a role in axonal conduction and synaptic transmission. Recently it has been reported that local anaesthetics depress influx of calcium ions at concentrations required to block nerve conduction [1, 2].

Calcium channel blockers block sodium in addition to calcium channels [3] and have local anaesthetic actions [4, 5]. Interaction between calcium channel blockers and local anaesthetic agents is now well documented [6, 7]. We have also reported that intrathecally administered verapamil potentiated the depth and duration of spinal anaesthesia with lignocaine [8]. Therefore, we hypothesized that co-administration of calcium channel blocking agents would increase the analgesic effects of local anaesthetics.

In this study we examined if calcium channel blockers could potentiate and prolong sensory block with lignocaine at peripheral nerves in rats.

Materials and methods

The study was approved by our Animal Care and Use Committee. Male Sprague–Dawley rats, weighing 250–300 g, were used in the experiments. Animals were housed in a temperature-controlled (21 ± 1 °C) room with a 21-h light-dark cycle (lights on 07:00 to 19:00) and given free access to food and water. To reduce the effects of handling on nociceptive responses, all animals were handled and trained in the test situation for at least 3 days before testing. A maximum of three experiments was conducted on each rat with a minimum of 3 days between studies.

NOCICEPTIVE TEST

To assess the thermal nociceptive threshold, the standardized tail flick test was performed, using a restrain box, by monitoring latency to withdraw from a heat source (a 50-W projection lamp bulb) focused on a distal segment of the tail (KN-205E, Natume, Japan). A single control switch simultaneously activated the light and a timer. The time interval between switching on the light to flick of the tail was recorded as tail flick latency. The location on the tail stimulated was varied systematically so that

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the same portion of the tail was not exposed repeatedly to the light source. A 10-s cut-off time was used in the tail flick tests to minimize tissue damage. Mean baseline tail flick latency was 3.2 (2.8–3.9) s in the experiment.

DRUGS AND INJECTION

The drugs used were lignocaine hydrochloride (Fujisawa, Osaka, Japan), verapamil hydrochloride (MW 491.07; Sigma, St Louis, MO, USA), diltiazem hydrochloride (MW 450.99; Tanabe, Osaka, Japan) and nicardipine hydrochloride (MW 515.99; Yamanouchi, Tokyo, Japan). Drugs were freshly dissolved in sterile physiological saline in concentrations that allowed local injection at the root of the tail in 100- μl volumes. Animals were placed in individual plastic cylinders with an opening to allow the tail to protrude. After determining baseline tail flick latencies, 0.3 % lignocaine alone, or combined with verapamil 25, 100 or 200 μg, diltiazem 25, 100 or 200 μg, or nicardipine 0.5, 1.0 or 2.0 μg, and verapamil 200 μg, diltiazem 200 μg or nicardipine 2.0 μg alone were injected bilaterally at the base of the tail in 200-μl volumes, in a randomized manner. Using the modified methods of Grant and colleagues [9], two 100-μl of volumes of each drugs were injected directly into the base of the animal's tail on opposite sides of the midline using a 30-gauge needle attached to a 100-μl syringe (Hamilton, Reno, NV, USA). Accurate bilateral injections were noted to result in slight circumferential swelling of the tail root, as described in an original report. Tail flick latencies were evaluated 5, 10, 15, 20, 30 and 45 min after administration of the drug at the root of the tail.

The pH values of the solutions of 0.3 % lignocaine, calcium channel blockers and mixtures of 0.3 % lignocaine and calcium channel blocker in physiological saline were analysed by an ABL3 (Radiometer, Copenhagen, Denmark). The pH of a 100-μl solution of verapamil, 200 μg, diltiazem 200 μg, nicardipine 2.0 μg, 0.3 % lignocaine–200 μg verapamil, 0.3 % lignocaine–200 μg diltiazem, and 0.3 % lignocaine–2.0 μg nicardipine were 5.81, 5.37, 5.28, 6.25, 6.01 and 5.59, respectively.

CARDIOVASCULAR VARIABLES AND TAIL TEMPERATURE

To examine cardiovascular variables and temperature in the tail, arterial pressure, heart rate and skin temperature at the middle of the tail were measured before and after administration of 0.3 % lignocaine–200 μg verapamil in the four animals in which an arterial catheter had been inserted via the internal carotid artery.

STATISTICAL ANALYSIS

The response for the tail flick test was calculated as percentage maximum possible effects (%MPE): %MPE = (post-drug latency − baseline latency)/(cut-off time − baseline latency) × 100 %. The area under the curve (AUC) of %MPE *vs* time was calculated using the trapezoidal rule in order to express the overall magnitude and duration of effect for the tail flick test. Differences in %MPE and AUC between groups, and within-group differences between baseline values and those after administration of the drugs, were tested using Friedman's analysis of variance (ANOVA) by ranks and the Mann-Whitney *U* test. $P < 0.05$ was considered statistically significant. All data are expressed as mean (SEM).

Results

Animals were able to move their tail at random throughout the experiments. Lignocaine 0.3 % alone, administered at the base of the tail, produced

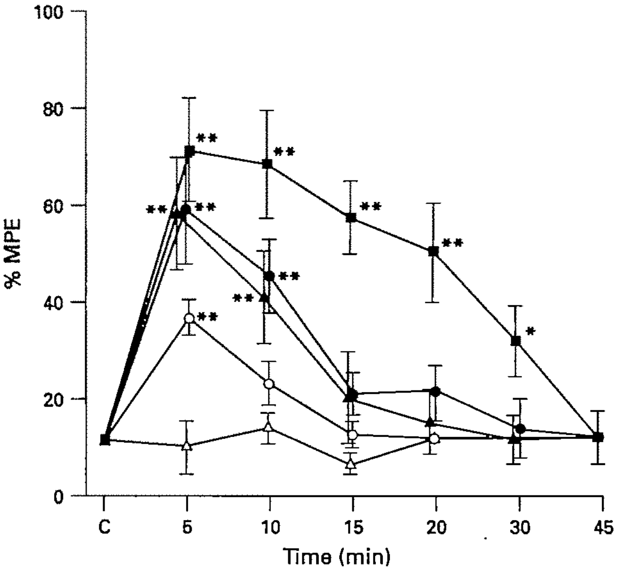

Figure 1 Changes in percentage maximum possible effect (% MPE) after injection of 0.3 % lignocaine (○, $n = 8$), verapamil 200 μg (△, $n = 5$) and a mixture of 0.3 % lignocaine and verapamil 200 μg (■, $n = 8$), 100 μg (●, $n = 6$) or 25 μg (▲, $n = 6$). Data are mean, SEM. *$P < 0.05$, **$P < 0.01$ compared with control (C) (pre-injection) value.

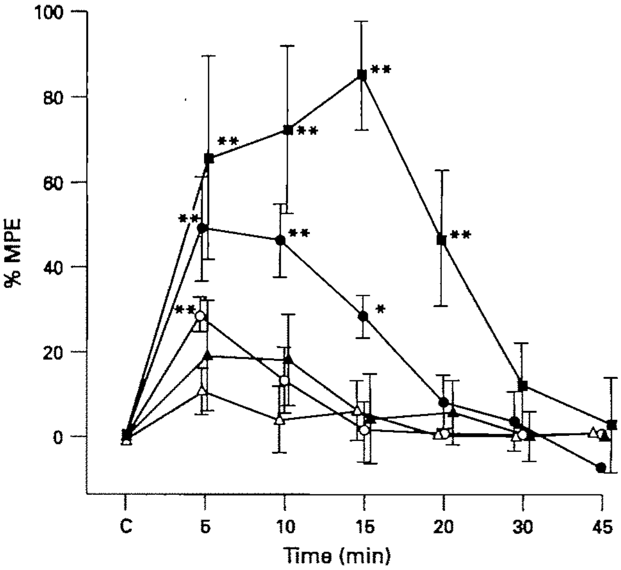

Figure 2 Changes in percentage maximum possible effect (% MPE) after injection of 0.3 % lignocaine (○, $n = 8$), diltiazem 200 μg (△, $n = 5$) and a mixture of 0.3 % lignocaine and diltiazem 200 μg (■, $n = 5$), 100 μg (●, $n = 5$) or 25 μg (▲, $n = 5$). Data are mean, SEM. *$P < 0.05$, **$P < 0.01$ compared with control (C) (pre-injection) value.

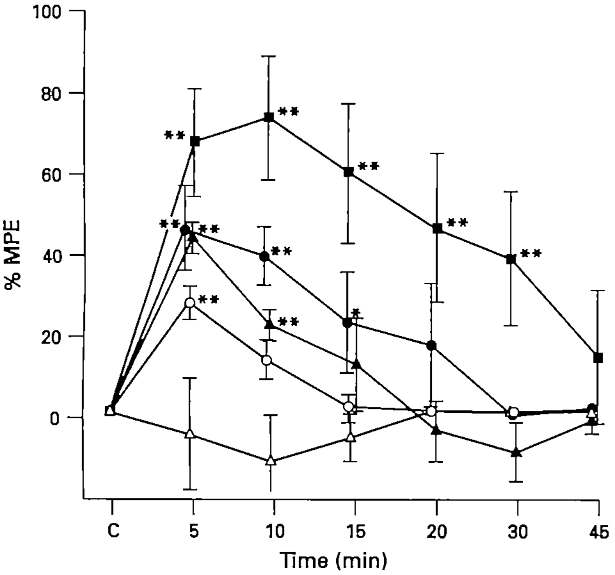

Figure 3 Changes in percentage maximum possible effect (% MPE) after injection of 0.3 % lignocaine (○, $n = 8$), nicardipine 2.0 µg (△, $n = 5$) and a mixture of 0.3 % lignocaine and nicardipine 2.0 µg (■, $n = 7$), 1.0 µg (●, $n = 5$) or 0.5 µg (▲, $n = 5$). Data are mean, SEM. *$P < 0.05$, **$P < 0.01$ compared with control (C) (pre-injection) value.

significant prolongation of tail flick latency. The peak effect was observed 5 min after drug administration. A large dose of calcium channel blocker (verapamil 200 µg, diltiazem 200 µg or nicardipine 2.0 µg) alone did not produce prolongation of tail flick latency compared with each pre-drug value.

In contrast, co-administration of lignocaine and the three different doses of verapamil produced a dose-dependent increase in tail flick latencies and the duration of sensory block increased with increasing concentration of verapamil compared with lignocaine alone (fig. 1).

A similar pattern of augmentation in % MPE and AUC after addition of different doses of diltiazem or nicardipine to 0.3 % lignocaine resulted in an increase in % MPE and AUC, which were approximately dose-dependent increases in the tail flick test (figs. 2–4).

There were no significant changes in mean arterial pressure, heart rate or tail temperature after local injection of the drugs at the base of the tail (data not shown).

Discussion

We have demonstrated that local sensory block of lignocaine was potentiated and prolonged by concomitantly administered L-type calcium channel blockers (which alone exert no influence on local sensory block) in a dose- and time-related manner.

Local anaesthetics such as lignocaine, procaine, amylocaine or cinchocaine have been shown to inhibit calcium uptake and the calcium ion-activated ATPase activity of sarcoplasmic reticulum vesicles [10–12]. This ability of local anaesthetic agents to inhibit calcium efflux from the sarcoplasmic reticulum was explained by incorporation of these amphophilic drugs into the lipid layer [13, 14], interaction with calcium ion binding sites on membrane phospholipids, or direct interaction with a calcium channel [15, 16].

Calcium channel blockers block sodium channels in addition to calcium channels in a dose-dependent manner and have local anaesthetic actions. Kraynack, Lawson and Gintautas demonstrated that a blocking action of the fast sodium channel by verapamil was almost equal to that of procaine, although the mode of pharmacological action of these drugs was different. It has also been demonstrated that simultaneous administration of an amide local anaesthetic agent and the calcium channel blocker, verapamil, has more marked cardiovascular depressant effect than local anaesthetic alone [6, 7]. In this study, a large dose of calcium channel blocker alone, administered into the base of the tail, produced no significant antinociceptive effects. It is therefore

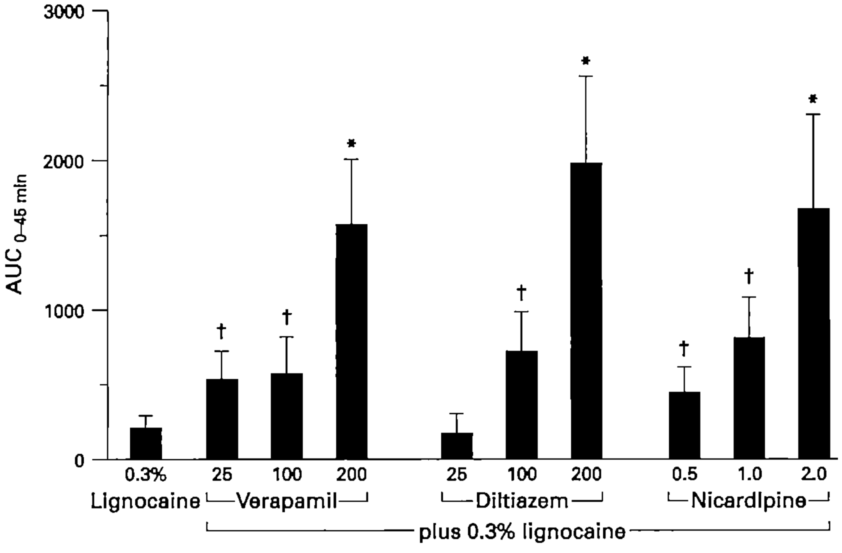

Figure 4 Area under the curve (AUC) of % MPE × time (0–45 min) after injection of 0.3 % lignocaine alone, and combined with verapamil 25, 100 or 200 µg, diltiazem 25, 100 or 200 µg or nicardipine 0.5, 1.0 or 2.0 µg. Data are mean, SEM. * $P < 0.05$, **$P < 0.01$ compared with 0.3 % lignocaine alone.

unlikely that the local anaesthetic activity of calcium channel blocking agents accounts for the increase in tail flick latency observed in the study, although little is known of the specific mechanism of augmentation of lignocaine sensory block by calcium channel blockers.

Several investigators have used *in vivo* animal models to evaluate local anaesthetic-induced conduction block. However, some of these studies have assessed sensory loss using non-quantitative methods. Analgesia tests in the rat using thermal stimulation such as tail flick or hot plate have been used for many years. These tests are useful for evaluation of systemic or neuroaxial analgesics but have limited use for local anaesthetics because they cannot clearly differentiate between motor and sensory block. A recent report has indicated that local anaesthetic injection directly into the base of the tail is a simple and reliable *in vivo* laboratory method using the standard tail flick test for comparing sensory block produced by different local anaesthetics [9]. These injections produce no motor block as tail motion is controlled by ligaments originating in muscles proximal to the level of the injection sites. Thus, the model enabled us to assess independently local sensory block produced by the injected drugs. In our study, all animals were able to move their tail at random after injection of the drugs.

It has been known widely that systemic administration of calcium channel blocker causes vasodilatation and cardiac depression, which result in hypotension and bradycardia [17]. No significant circulatory changes were observed in that study. Another possibility that could explain the observed effects would be a pharmacokinetic interaction between the drug solutions, such as changes in the pH of the tissue of the injection sites. Concomitant administration of lignocaine and calcium channel blockers might produce pharmacodynamic changes in tail temperature or regional blood flow. It is also not enough to explain the fact that local lignocaine sensory block was potentiated by co-administration of calcium channel blockers because administration of a large dose of calcium channel blockers alone did not produce a significant change in tail flick latency, as described above.

In this study we used three different calcium channel blockers with different structures: diphenylalkylamine (verapamil), benzothiazepine (diltiazem) and dihydropyridine (nicardipine). ID_{50} values for maximum amplitude of the calcium ion inward current in ileum smooth muscle of rabbits have been reported as 1.4 μmol litre^{-1}, 1.3 μmol litre^{-1} and 24 nmol litre^{-1} for verapamil, diltiazem and nicardipine, respectively [18]. Although the doses of calcium channel blockers co-administered in the study may not be exactly equipotent on neuronal calcium channels, similar patterns of augmentation of local sensory block of lignocaine by the three different structures of calcium channel blockers were demonstrated. These results suggest that the potentiation observed in the study was probably caused by direct inhibition of voltage-dependent calcium conductance, and consequent lowering of calcium ions of the peripheral nerves.

In conclusion, we have demonstrated that co-administration of a calcium channel blocker potentiated the degree and duration of local lignocaine sensory block. Most local anaesthetic drugs can be used for peripheral nerve block and the choice of drug is determined primarily by the required duration of anaesthesia. The duration of sensory analgesia is prolonged significantly when vasoconstrictors, usually adrenaline, are frequently added to local anaesthetic solutions. However, addition of a vasoconstrictor may cause cardiovascular disturbances, including cardiac arrhythmia or hypertension. The use of mixtures of local anaesthetic and calcium channel blocker may offer clinical advantages, with peripheral nerve block for chronic pain management. However, more study is required before co-administration of lignocaine and calcium channel blockers can be considered for clinical use.

References

1. Frelin C, Vibne P, Lazdunski M. Biochemical evidence for pharmacological similarities between α-adrenoreceptors and voltage-dependent Na^+ and Ca^{++} channels. *Biochemical and Biophysical Research Communications* 1982; **106**: 967–973.
2. Palade PT, Almers W. Slow calcium and potassium currents in frog skeletal muscle: their relationship and pharmacologic properties. *Pflugers Archiv. European Journal of Physiology* 1985; **405**: 91–101.
3. Ragsdale DS, Scheuer T. Catterall WA. Frequency and voltage-dependent inhibition of type IIA Na^+ channels, expressed in a mammalian cell line, by local anesthetic, antiarrhythmic, and anticonvulsant drugs. *Molecular Pharmacology* 1991; **40**: 756–765.
4. Kraynack BJ, Lawson NW, Gintautas J. Local anesthetic effect of verapamil in vitro *Regional Anesthesia* 1982; **7**: 114–117.
5. Singh BN, Vaughan Williams EM. A fourth class of antidysrhythmic action? Effect of verapamil on ouabain toxicity, on arterial and ventricular intracellular potentials, and on other features of cardiac function. *Cardiovascular Research* 1972; **6**: 109–119.
6. Kapur PA, Grogan DL, Fournier DJ. Cardiovascular interactions on lidocaine with verapamil or diltiazem in the dog. *Anesthesiology* 1988; **68**: 79–85.
7. Edouard AR, Berdeaux A, Ahmad R, Samii K. Cardiovascular interaction of local anesthetics and calcium entry blockers in conscious dogs. *Regional Anesthesia* 1991; **16**: 95–100.
8. Omote K, Iwasaki H, Kawamata M, Satoh O, Namiki A. Effects of verapamil on spinal anesthesia with local anesthetics. *Anesthesia and Analgesia* 1995; **80**: 444–448.
9. Grant GJ, Zakowski MI, Vermeulen K, Langerman L, Ramanathan S, Turndorf H. Assessing local anesthetic effect using the mouse tail flick test. *Journal of Pharmacological and Toxicological Methods* 1993; **29**: 223–226.
10. Coyle DE, Sperelakis N. Bupivacaine and lidocaine blockade of calcium-mediated slow action potentials in guinea pig ventricular muscle. *Journal of Pharmacology and Experimental Therapeutics* 1987; **242**: 1001–1005.
11. Katz AM, Repke DI, Corkedale S, Schwarz J. Effects of local anesthetics on calcium transport by canine cardiac microsomes (fragmented sarcoplasmic reticulum). *Cardiovascular Research* 1975; **9**: 764–768.
12. Balzer H. The effect of quinidine and drugs with quinidine-like action (propranolol, verapamil and tetracaine) on the calcium transport system in isolated sarcoplasmic reticulum vesicles of rabbit skeletal muscle. *Naunyn-Schmeideberg's Archives of Pharmacology* 1972; **274**: 256–272.
13. Seeman P. The membrane actions of anesthetics and tranquilizers. *Physiological Reviews* 1972; **24**: 582–655.
14. Roth S, Seeman P. Anesthetics expand erythrocyte mem-

branes without causing loss of K$^+$. *Biochimica et Biophysica Acta* 1972; **255**: 190–198.

15. Kawant WD, Seeman P. The displacement of membrane calcium by a local anesthetic (chlorpromazine). *Biochimica et Biophysica Acta* 1969; **193**: 338–349.
16. Feinstein MB. Reaction of local anesthetics with phospholipids. A possible chemical basis for anesthesia. *Journal of General Physiology* 1964; **48**: 357–374.
17. Omote K, Kirita A, Namik A, Iwasaki H. Effects of nicardipine on the circulatory responses to tracheal intubation in normotensive and hypertensive patients. *Anaesthesia* 1992; 47: 24–27.
18. Terada K, Kitamura K, Kuriyama H. Blocking actions of Ca^{++} antagonists on the Ca^{++} channels in the smooth muscle cell membrane of small intestine. *Pflugers Archiv. European Journal of Physiology* 1987; **408**: 552–557.

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I.v. anaesthetic agents inhibit dihydropyridine binding to L-type voltage-sensitive Ca^{2+} channels in rat cerebrocortical membranes†

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Summary

Previous studies have implicated the neuronal L-type voltage-sensitive Ca^{2+} channel (VSCC) as a target site for i.v. anaesthetic agents. It is unclear if these agents interact with the L-channel α-subunit 1,4-dihydropyridine (DHP) binding site. In this study, we have examined the interaction of thiopentone, pentobarbitone, ketamine, etomidate, propofol and alphaxalone, and the non-anaesthetic barbiturate, barbituric acid, with the DHP binding site on rat cerebrocortical membranes. Binding assays were performed in 1-ml volumes of Tris-HCl 50 mmol litre^{-1}, pH 7.4, for 90 min at room temperature containing 200 μg of membrane protein with [^{3}H]PN200-110 as a radiolabelled DHP. Non-specific binding was defined in the presence of nifedipine 10^{-6} mol litre^{-1}. The interaction of i.v. anaesthetics was determined by displacement of [^{3}H]PN200-110 0.2 nmol litre^{-1}. All i.v. anaesthetics showed some interaction with the DHP binding site. The concentrations of anaesthetic producing 25% inhibition of specific binding (corrected for the competing mass of [^{3}H]PN200-110), K_{25} were (μmol litre^{-1}): thiopentone 48 (SEM 2), pentobarbitone 95 (7), propofol 40 (2), etomidate 25 (2), alphaxalone 17 (3) and ketamine 198 (16). Barbituric acid was ineffective. With the exception of ketamine, there was a significant correlation between K_{25} and peak serum concentration during anaesthesia ($P = 0.033$) and serum concentrations on wakening ($P = 0.018$), suggesting that the L-channel DHP binding site may be a target for i.v. anaesthetic agents. (*Br. J. Anaesth.* 1996; **77**: 248–253)

Key words

Anaesthetics i.v. Ions, ion channels. Ions, calcium. Model, rat.

Neuronal L-type voltage-sensitive Ca^{2+} channels are located predominantly on neuronal cell bodies and are involved in the regulation of neurotransmitter release [1]. Moreover, L-type Ca^{2+} channel blockers potentiate anaesthetic potency *in vivo* [2–6]. These findings suggest that L-type voltage-sensitive Ca^{2+} channels may be a target site for general anaesthetic agents. Indeed, i.v. anaesthetics are known to interact with 1,4-dihydropyridine (DHP) binding sites on L-type Ca^{2+} channels in skeletal [7] and smooth muscle [8], and there is evidence to suggest that i.v. anaesthetics inhibit neuronal L-type Ca^{2+} channels [9, 10]. It is still unclear, however, if i.v. anaesthetic agents interact directly with DHP binding sites on the α_1 subunit of neuronal L-type Ca^{2+} channels. In contrast, the interaction of volatile general anaesthetic agents is well documented [11, 12]. In this study, we examined if a range of i.v. anaesthetic agents interact with the DHP binding site (labelled with (+)-[methyl-^{3}H]PN200-110, (+)-[methyl-^{3}H]isopropyl-4-(2,1,3-benzoadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate) on neuronal L-type Ca^{2+} channels in rat cerebrocortical membranes.

Materials and methods

TISSUE PREPARATION

Female Wistar rats (250–300 g) were stunned and then decapitated. The brain was removed rapidly, the cerebrocortex detached from its internal structures, placed in Tris HCl 50 mmol litre^{-1}, pH 7.4 at 4 °C, and homogenized using a tissue tearor (setting 5,5 × 30-s bursts). The resulting homogenate was centrifuged at 18000 *g* for 10 min and the pellet resuspended in Tris HCl buffer. This procedure was repeated three times. Membranes were frozen in aliquots at −40 °C.

MEASUREMENT OF [^{3}H]PN200-110 BINDING

All binding assays were performed in 1-ml volumes of Tris HCl buffer for 90 min (the optimal incubation time was determined empirically) at 20 °C using cerebrocortical membranes (approximately 200 μg of protein). Saturation analyses to determine the equilibrium dissociation constant (K_d) and the maximal binding capacity (Bmax) were performed using increasing concentrations of [^{3}H]PN200-110 (0.02–2.0 nmol litre^{-1}). In this method, as the concentration of label increases, the binding sites

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saturate (analogous to saturation of an enzyme reaction for determination of K_m and Vmax) and the concentration at which specific binding saturates is used to determine Bmax (see fig. 1). It follows that the concentration of ligand that yields half the Bmax is the K_d. Non-specific binding was defined in the presence of excess (10^{-5} mol litre^{-1}) nifedipine. After incubation, each sample was filtered under vacuum through Whatman GF/B filters using a Brandel cell harvester to separate bound and free radioactivity. Filter retained (bound) radioactivity was extracted for at least 8 h in 4 ml of scintillation fluid before estimation using a beta scintillation counter. The estimated radioactivity was quench corrected with an average [^{3}H] counting efficiency of 60.4%. In order to determine if an agent interacted with L-type Ca^{2+} channels, the dihydropyridine binding site was labelled with [^{3}H]PN200-110. Increasing concentrations of unlabelled displacer (anaesthetic agents) were then added. Displacement of [^{3}H]PN200-110 binding by the anaesthetic agents indicates that they are interacting at the same site as the radiolabel, that is the α_1 subunit of the L-type Ca^{2+} channel. A fixed concentration of [^{3}H]PN200-110 (0.2 nmol litre^{-1}) was displaced by the following unlabelled agents: thiopentone ($n = 6$; 10^{-7}–10^{-3} mol litre^{-1}), pentobarbitone ($n = 6$; 10^{-7}–10^{-3} mol litre^{-1}), ketamine ($n = 6$; 10^{-4}–10^{-2} mol litre^{-1}, $n = 4$; 10^{-7}–10^{-3} mol litre^{-1}), etomidate ($n = 6$; 3×10^{-7}–10^{-4} mol litre^{-1}), propofol ($n = 6$; 3×10^{-7}–10^{-4} mol litre^{-1}) and alphaxalone ($n = 6$; 3×10^{-7}–10^{-4} mol litre^{-1}). A non-anaesthetic barbiturate, barbituric acid ($n = 6$; 10^{-7}–10^{-3} mol litre^{-1}) and nifedipine ($n = 5$; 10^{-5}–3×10^{-13} mol litre^{-1}) were examined as negative and positive controls, respectively. Agents were dissolved in Tris HCl buffer as follows; thiopentone (100 mmol litre^{-1} stock in NaOH 0.1 mol litre^{-1}), pentobarbitone and barbituric acid (50 mmol litre^{-1} stock in distilled water), propofol (100 mmol litre^{-1} stock in DMSO), alphaxalone and nifedipine (50 mmol litre^{-1} stock in DMSO), etomidate (50 mmol litre^{-1} stock in HCl 0.1 mol litre^{-1}) and ketamine (500 mmol litre^{-1} stock in distilled water). Appropriate solvent concentrations were added to control tubes. In addition, a full dose–response curve for the effects of DMSO ($n = 6$) was constructed and indicated that 1% DMSO, which is the highest concentration used in these studies, produced only 3±1% displacement. The highest anaesthetic concentration used was limited by agent solubility.

DATA ANALYSIS

Specific binding was calculated as the difference between total and non-specific binding. Bmax and K_d were obtained from Scatchard plots. In displacement studies, the concentrations of displacer producing 25% and 50% displacement of specific binding (IC_{25} and IC_{50}) were obtained by computer-assisted curve fitting (Graphpad-Prism) and corrected for the competing mass of [^{3}H]PN200-110 according to Cheng and Prusoff [13] to yield the affinity constant (K_{25} and K_{50}). All data are expressed as mean (SEM).

Results

Binding of [^{3}H]PN200-110 was time- (fig. 1A) and dose- (fig. 1B) dependent. Bmax and K_d values estimated from Scatchard plots (fig. 1C) were 152 (14) fmol/mg protein and 59 (3) pmol litre^{-1}, re-

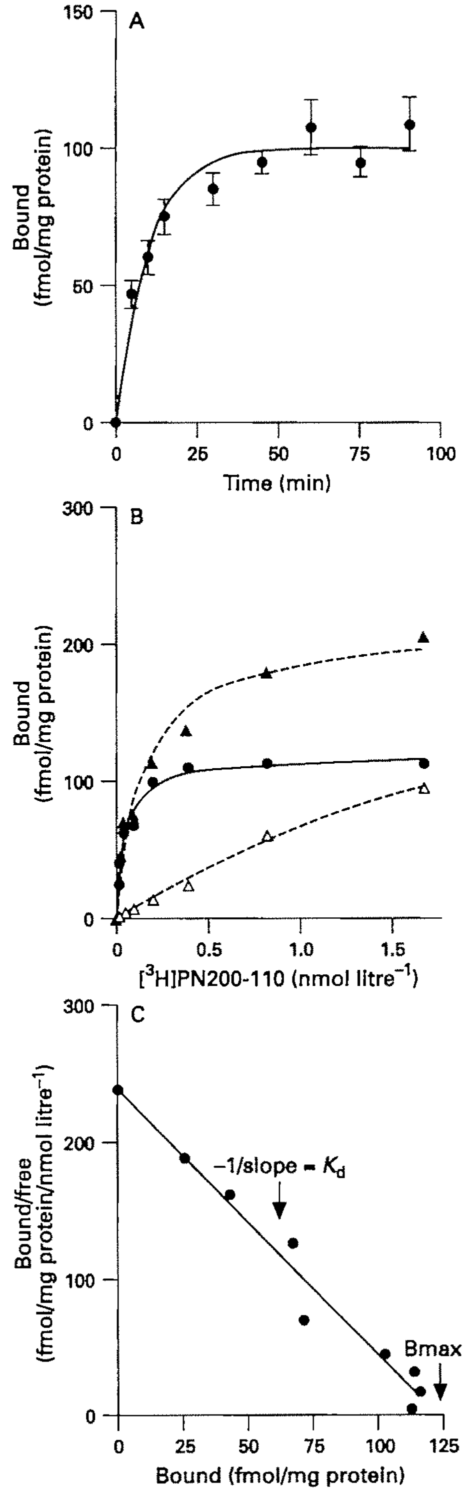

Figure 1 Binding of [^{3}H]PN200-110 to rat cerebrocortical membranes was time- (A) and dose- (B) dependent. In A, [^{3}H]PN200-110 concentration was approximately 0.2 nmol litre^{-1}. C = Scatchard transformation of the specific binding curve in B (● = specific, ▲ = total and △ = non-specific binding) and was used to determine Bmax and K_d. Data are mean, SEM ($n = 5$) in A and from a representative experiment (from $n = 5$) in B and C.

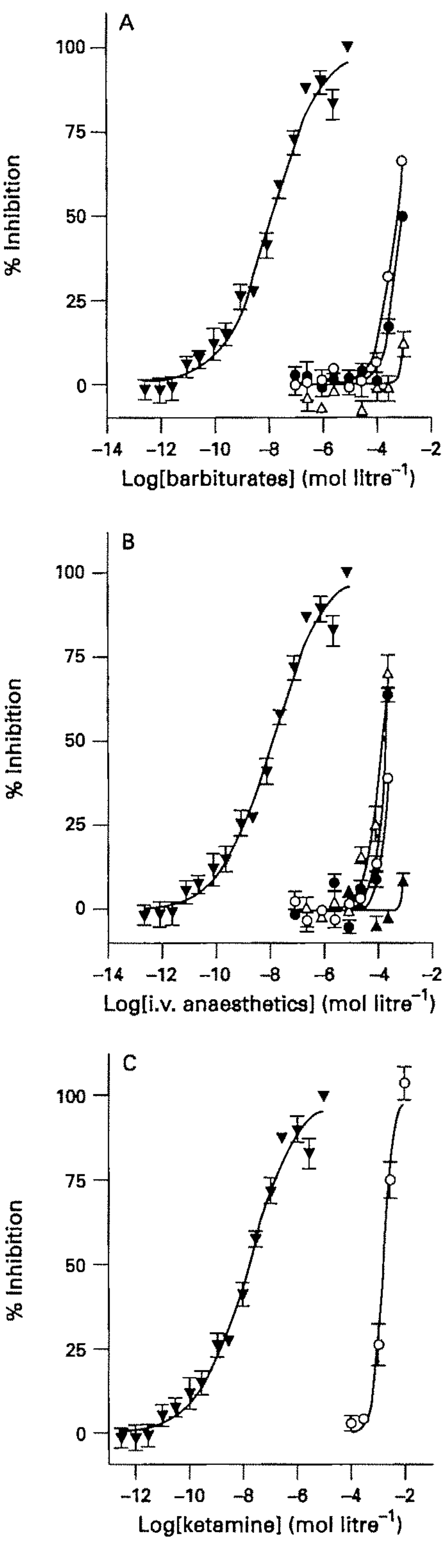

Figure 2 [^{3}H]PN200-110 binding (approximately 0.2 nmol litre^{-1}) was displaced dose-dependently by anaesthetic barbiturates (thiopentone (○), pentobarbitone (●), barbituric acid (△)) (A), propofol (○), etomidate (●), alphaxalone (△) and ketamine (▲) at anaesthetic concentrations (B) and ketamine (○) at local anaesthetic concentrations (C). Nifedipine (▼) is included as a high affinity reference compound. Data are mean, SEM (n = 4–6).

spectively. Nifedipine displaced [^{3}H]PN200-110 binding with a K_{50} of 3.2 (0.6) nmol litre^{-1} (n = 5). All i.v. anaesthetics displaced specific [^{3}H]PN200-110 binding in a dose-dependent manner (fig. 2A–C)

Table 1 Effects of anaesthetics on [^{3}H]PN200-110 binding (mean (SEM))

Agent	n	K_{50} (µmol litre^{-1})	K_{25} (µmol litre^{-1})
Thiopentone	6	134 (6)	48 (2)
Pentobarbitone	6	211 (6)	95 (7)
Propofol	6	97 (5)	40 (2)
Etomidate	6	36 (1)	25 (2)
Alphaxalone	6	34 (5)	17 (3)
Ketamine	6	377 (49)	198 (16)

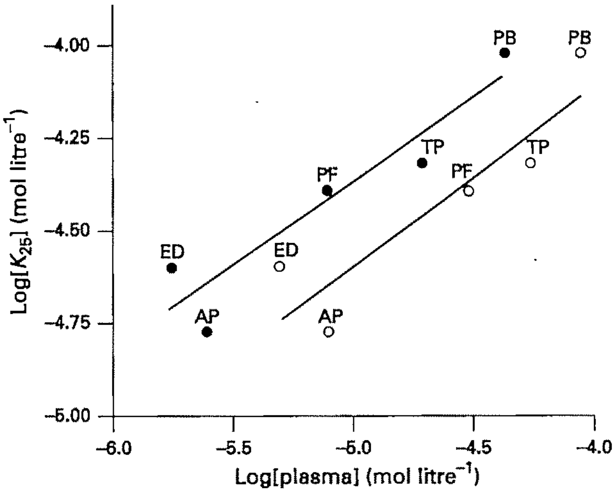

Figure 3 Correlation between binding K_{25}, peak serum concentrations and wakening plasma concentrations of alphaxalone (AP), etomidate (ED), propofol (PF), thiopentone (TP) and pentobarbitone (PB). ● = Awake ($r^2 = 0.0880$, $P = 0.0184$), ○ = peak ($r^2 = 0.824$, $P = 0.0333$).

with K_{25} and K_{50} values shown in table 1. Barbituric acid was ineffective. Ketamine displaced [^{3}H]PN200-110 only at high, local anaesthetic concentrations [14, 15] (fig. 2C). With the exception of ketamine, there was a significant correlation between K_{25} ($r^2 = 0.834$, $P = 0.0333$) (fig. 3) and K_{50} ($r^2 = 0.960$, $P = 0.0035$) and peak plasma concentrations during anaesthesia [16–18]. In addition, there was a significant correlation between plasma concentrations on wakening and both K_{25} ($r^2 = 0.843$, $P = 0.0278$) and K_{50} ($r^2 = 0.965$, $P = 0.0028$) (fig. 3).

Discussion

In this study, our data suggest that i.v. anaesthetic agents interact with the DHP binding site on neuronal L-channels based on the observed correlation between K_{25} and K_{50} and peak plasma concentrations during major surgery or deep sedation [16–18], and plasma concentrations seen on awakening from anaesthesia [17, 19, 20]. Recent reports, however, have suggested that the GABA$_A$ receptor may represent a critical target site for general anaesthesia with voltage-sensitive Ca^{2+} channels being less or unimportant as several anaesthetics produce stereospecific inhibition of Cl$^-$ flux through the GABA$_A$ receptor and the IC$_{50}$ for Ca^{2+} channel inhibition by volatile anaesthetic agents exceeds MAC [19]. One important question for consideration is what degree of inhibition is clinically relevant?

Should a comparison with 50 % inhibition of *in vitro* events be made? It is inconceivable that the central nervous system or cardiovascular system could withstand this degree of inhibition, yet this comparison has been made (e.g. MAC in the whole animal compared with IC_{50} channel activity [19]). Several studies [19, 21, 22] have suggested that clinically relevant concentrations of anaesthetics inhibit neurotransmitter release with only 20–30 % inhibition in Ca^{2+} entry. We have therefore argued that it may be more relevant to compare lower degrees of inhibition, for example 25 % [23]. The data in this article used total peak serum concentrations and those seen on wakening [16–20]. After accounting for varying degrees of protein binding the free drug concentration would be lower. It has been suggested that the relevant anaesthetic concentration for *in vitro* studies is the free (unbound) aqueous concentration at the appropriate end-point for general anaesthesia. However, it should be borne in mind that many i.v. anaesthetic agents [24–27] are concentrated in the brain and their concentration at the target site (the channel) may be similar to the concentration in the brain. As only unbound anaesthetics can pass through the blood–brain barrier, the degree of protein binding is clearly important. However, we should also consider that a new equilibrium which restores the free concentration occurs after a proportion of the free anaesthetic has left the plasma and entered the brain. Therefore, both free and bound (as a pool to replenish the free drug) anaesthetics could be available for diffusion, although the diffusion rate must be dependent on free concentration [28]. In our study, displacement of [^{3}H]PN200-110 binding with i.v. anaesthetics was measured at 90 min (a time at which equilibrium with the brain would have occurred), and therefore we feel that "total" drug concentration may reflect that seen at the target site in the brain. Interestingly, Winters and colleagues [29] examined the influence of albumin on thiopentone action in the rat. In their study they showed that although albumin 400 mg kg^{-1} i.v. 15 min before thiopentone reduced the sleeping time by 30 % ($P < 0.01$), the awake concentration of thiopentone in the brain and total plasma concentration was not affected. If only the free concentration is important, a higher plasma concentration of thiopentone at awakening would be expected in the albumin group. Although their study supports our hypothesis, detailed studies are required to estimate accurately the true "at the target" concentration.

In this study we have compared the K_{50} obtained using rat brain with human serum concentrations during anaesthesia. Although anaesthetic requirements differ between species, there is still close correlation for anaesthetic potencies between species (e.g. a good correlation exists between human MAC and mouse ED_{50} to abolish the righting reflex [30]). Therefore, we suggest that the K_{50} obtained in this study using rat cerebrocortical membranes is likely to be comparable with human serum concentrations.

Several *in vivo* studies [3–5] have suggested that the neuronal L-type Ca^{2+} channel DHP binding site may be involved in the mechanism of general anaesthesia. Dolin and co-workers found that the DHP L-type Ca^{2+} channel blocker, nitrendipine, increased the general anaesthetic potencies of ethanol and pentobarbitone [3], and benzodiazepines [4], while the DHP L-channel activator, Bay K 8644, reduced the anaesthetic action of benzodiazepines [4]. Horvàth, Szikszay and Benedek [5] also reported that Bay K 8644 significantly increased the onset time of hypnosis and decreased the anaesthetic potency of dexmedetomidine, while verapamil (L-channel blocker) significantly augmented the hypnotic–anaesthetic action. However, if L-channels are target sites for anaesthetic agents then why are L-channel blockers not anaesthetic agents in their own right? This may be explained by poor access to the brain for some L-channel blockers [31]. Interestingly, in a long-term, multicentre study, flunarizine, a non-selective Ca^{2+} channel antagonist which does pass the blood–brain barrier, was reported to produce somnolence as a side effect in 42 % of migraine patients [32]. In addition, L-channel blockers have been reported to exert an antinociceptive action, which is an important component of general anaesthesia, for both rats and humans [33–36]. Electrophysiological studies also showed that pentobarbitone [9] and propofol [10] inhibited neuronal L-type Ca^{2+} channels. Moreover, volatile anaesthetics have been reported to inhibit the DHP binding site in rat brain membranes [11, 12] consistent with our hypothesis. Collectively we feel that these data suggest that the DHP binding site on the L-type voltage sensitive Ca^{2+} channel may be a target site for general anaesthetic agents.

Ketamine could only inhibit DHP binding at concentrations in excess of those required to produce general anaesthesia. However, ketamine has local anaesthetic properties because it can produce not only general anaesthesia but also local anaesthesia (such as i.v. regional anaesthesia) [14, 37]. Durrani and colleagues [14] reported that > 0.3 % ketamine (approximately 10^{-2} mol $litre^{-1}$) produced adequate regional anaesthesia with complete sympathetic, sensory and motor block. These concentrations are in agreement with our studies and suggest that the local anaesthetic action of ketamine may include Ca^{2+} channel block. Clearly a wide range of local anaesthetic agents will need to be examined to confirm or refute this hypothesis, although recent studies suggest that Ca^{2+} channels may be involved in the mechanism of action of local anaesthetics [38, 39]. It should also be noted that ketamine is an exception to the "GABA" hypothesis in that this agent does not interact with $GABA_A$ receptors [19]. As ketamine is a non-competitive NMDA channel blocker [40] it is possible that this agent could similarly block the aqueous pore of the L-channel. Indeed, channel block by ketamine is supported by the observed inhibition of K^+-evoked noradrenaline release from SH-SY5Y human neuroblastoma cells [41] with simultaneous inhibition of K^+-evoked Ca^{2+} entry. Does inhibition of DHP binding correlate with inhibition of Ca^{2+} influx? Certainly, Toll [42] showed, using PC12 cells, that the IC_{50} of nifedipine (2.7 (0.3) nmol $litre^{-1}$) for $^{45}Ca^{2+}$ uptake was similar to that (1.6 (0.4) nmol $litre^{-1}$) of [^{3}H]nitrendipine binding. Other investigators have also suggested that nifedipine reduces Ca^{2+} influx, with IC_{50} values using neuronal cells such as NCB-20 cells [43], NG08-15 cells [44] and PC12 cells [21] similar to the K_{50} reported here. However, while we suspect that DHP displacement with anaesthetic agents may produce a similar reduction in Ca^{2+} influx we have no data in this tissue to support this notion. However, in SH-SY5Y human neuroblastoma cells we have shown [45] that thiopentone and propofol inhibited K^+-evoked increases in intracellular Ca^{2+} with IC_{50} values of 121 and 124 µmol litre^{-1}, respectively, in good agreement with the K_{50} values also reported here.

In conclusion, we suggest that the DHP binding site of L-type voltage sensitive Ca^{2+} channels may be a target site for i.v. anaesthetic agents.

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References

1. Spedding M, Lepagnol J. Pharmacology of sodium and calcium channel modulation in neurons: implications for neuroprotection. *Biochemical Society Transactions* 1995; **23**: 633–636.
2. Maze M, Mason DM, Kates RE. Verapamil decreases MAC for halothane in dogs. *Anesthesiology* 1983; **59**: 327–329.
3. Dolin SJ, Little HJ. Augmentation by calcium channel antagonists of general anaesthetic potency in mice. *British Journal of Pharmacology* 1988; **88**: 909–914.
4. Dolin SJ, Patch TL, Rabbani M, Taberner PV, Little HJ. Differential interactions between benzodiazepines and the dihydropyridines, nitrendipine and Bay K 8644. *Neuropharmacology* 1991; **30**: 217–224.
5. Horvàth G, Szikszay M, Benedek G. Calcium channels are involved in the hypnotic–anesthetic action of dexmedetomidine in rats. *Anaesthesia and Analgesia* 1992; **74**: 884–888.
6. Shen Y, Sangiah S. Effect of cadmium and verapamil on ketamine-induced anesthesia in mice. *Veterinary and Human Toxicology* 1995; **37**: 201–203.
7. Fruen BR, Mickelson JR, Roghair T, Litterer LA, Louis CF. Effects of propofol on Ca^{2+} regulation by malignant hyperthermia-susceptible muscle membranes. *Anesthesiology* 1995; **82**: 1274–1282.
8. Hirota K, Zsigmond EK, Matsuki A, Rabito SF. Ketamine inhibits contractile responses of intestinal smooth muscle by decreasing the influx of calcium through the L-type calcium channel. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 759–764.
9. Gross RA, Macdonald RL. Differential actions of pentobarbitone on calcium current component of mouse sensory neurones in culture. *Journal of Physiology (London)* 1988; **405**: 187–203.
10. Olcese R, Usai C, Maestrone E, Nobile M. The general anesthetic propofol inhibits transmembrane calcium current in chick sensory neurons. *Anaesthesia and Analgesia* 1994; **78**: 955–960.
11. Moody EJ, Harris B, Hoehner P, Skolnick P. Inhibition of [^{3}H]isradipine binding to L-type calcium channels by the optical isomers of isoflurane. *Anesthesiology* 1994; **81**: 124–128.
12. Drenger B, Heitmiller ES, Quigg M, Blank TJ. Depression of calcium channel blocker binding to rat brain membranes by halothane. *Anaesthesia and Analgesia* 1992; **74**: 758–761.
13. Cheng YC, Prusoff WM. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochemical Pharmacology* 1973; **22**: 3099–3108.
14. Durrani Z, Winnie AP, Zsigmond EK, Burnett ML. Ketamine for intravenous regional anaesthesia. *Anaesthesia and Analgesia* 1989; **68**: 328–332.
15. Reves JG, Glass PSA, Lubarsky DA. Non barbiturate intravenous anesthetics. In: Miller RD, ed. *Anaesthesia*, 4th Edn. New York: Churchill-Livingston, 1994; 247–289.
16. Bayliff CD, Schwartz ML, Hardy BG. Pharmocokinetics of high-dose pentobarbital in severe head trauma. *Clinical Pharmacology and Therapeutics* 1985; **38**: 457–461.
17. Glass PSA, Shafer SL, Jacobs JR, Reves JG. Intravenous anesthetic delivery. In: Miller RD, ed. *Anaesthesia*, 4th Edn. New York: Churchill-Livingstone, 1994; 389–416.
18. Bendtsen A, Kruse A, Madsen JB, Astrup J, Rosenørn J, Blatt-Lyon B, Cold GE. Use of continuous infusion of althesin in neuroanaesthesia. *British Journal of Anaesthesia* 1985; **57**: 369–374.
19. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; **367**: 607–614.
20. Savege TM, Zych Z, Dubois M. The relationship between the peak of the cerebral function monitor trace, consciousness and blood concentration of alphaxalone. *British Journal of Anaesthesia* 1978; **50**: 1085P.
21. Kress HG, Müller J, Eisert A, Glige U, Tas PW, Koschel K. Effects of volatile anesthetics on cytoplasmic Ca^{2+} signalling and transmitter release in a neuronal cell line. *Anesthesiology* 1991; **74**: 309–319.
22. Miao N, Frazer MJ, Lynch C III. Volatile anesthetics depress Ca^{2+} transients and glutamate release in isolated cerebral synaptosomes. *Anesthesiology* 1995; **83**: 593–603.
23. Hirota K, Lambert DG. Voltage sensitive Ca^{2+} channels and anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 344–346.
24. Baekeland F, Greene NM. Effect of diethyl ether on tissue distribution and metabolism of pentobarbital in rats. *Anesthesiology* 1958; **19**: 724–732.
25. Cohen ML, Chan SL, Way WL, Trevor AJ. Distribution in the brain and metabolism of ketamine in the rat after intravenous administration. *Anesthesiology* 1973; **39**: 370–376.
26. Heykants JJP, Meuldermans WEG, Michiels LJM, Lewi PJ, Janssen PA. Distribution, metabolism and excretion of etomidate, a short-acting hypnotic drug, in the rat. Comparative study of (R)-(+) and (S)-(−)-etomidate. *Archives Internationales de Pharmacodynamie et de Thérapie* 1975; **216**: 113–129.
27. Shyr MH, Tsai TH, Tan PPC, Chen CF, Chan SHH. Concentration and regional distribution of propofol in brain and spinal cord during propofol anaesthesia in the rat. *Neuroscience Letters* 1995; **184**: 212–215.
28. Hull CJ. Pharmacokinetics and pharmacodynamics, with particular reference to intravenous anaesthetic agents. In: Nunn JF, Utting JE, Brown BR jr, eds. *General Anaesthesia*, 5th ed. London: Butterworths, 1989; 97–114.
29. Winters WD, Conard A, Lenartz HF, Blaskovics JB. Influence of corn oil, heparin and albumin on thiopental action in rats. *Anesthesiology* 1962; **23**: 27–31.
30. Koblin DD. Mechanism of action. In: Miller RD, ed. *Anaesthesia*, 4th ed. New York: Churchill Livingstone, 1994; 67–99.
31. Cherian L, Kurnvilla A, Abraham J, Chandy M. The effect of experimental spinal-cord injury on transfer of verapamil to CSF in monkeys. *Asia Pacific Journal of Pharmacology* 1992; **7**: 141–143.
32. Leone M, Grazzi L, Bussone G. Flunarizine in migraine—a minireview. *Headache* 1991; **31**: 388–391.
33. Carta F, Bianchi M, Argenton S, Cervi D, Marolla G, Tamburini M, Breda M, Fantoni A, Panerai AE. Effect of nifedipine on morphine-induced analgesia. *Anaesthesia and Analgesia* 1990; **70**: 493–498.
34. Miranda HF, Bustamante D, Kramer V, Pelissier T, Saavedra H, Paeile C, Fernandez E, Pinardi G. Antinociceptive effects of Ca^{2+} channel blockers. *European Journal of Pharmacology* 1992; **217**: 137–141.
35. Wong CH, Dey P, Yarmush J, Wu WH, Zbuzek VK. Nifedipine-induced analgesia after epidural injection in rats. *Anaesthesia and Analgesia* 1994; **79**: 298–302.
36. Santillan R, Maestre JM, Hurlé MA, Flórez J. Enhancement of opiate analgesia by nimodipine in cancer patients chronically treated with morphine: a preliminary report. *Pain* 1994; **58**: 129–132.

37. Amiot JF, Bouju PH, Palacci JH, Balliner E. Intravenous regional anaesthesia with ketamine. *Anaesthesia* 1985; **40**: 899–901.
38. Sugiyama K, Muteki T. Local anesthetics depress the calcium current of rat sensory neurons in culture. *Anesthesiology* 1994; **80**: 1369–1378.
39. Omote K, Iwasaki H, Kawamata M, Satoh O, Namiki A. Effects of verapamil on spinal anaesthesia with local anesthetics. *Anaesthesia and Analgesia* 1995; **80**: 444–448.
40. Brockmeyer DM, Kendig JJ. Selective effects of ketamine on amino acid-mediated pathways in neuronal rat spinal cord. *British Journal of Anaesthesia* 1995; 74: 79–84.
41. Sikand KS, Smith G, Lambert DG. Ketamine inhibits K^+ evoked [^{3}H]noradrenaline release from SH-SY5Y cells by reducing calcium influx. *Biochemical Society Transactions* 1995; 23: 417S.
42. Toll L. Calcium antagonists. High-affinity binding and inhibition of calcium transport in a clonal cell line. *Journal of Biological Chemistry* 1982; 257: 13189–13192.
43. Freedman SB, Dawson G, Villereal ML, Miller RJ. Identification and characterization of voltage-sensitive calcium channels in neuronal clonal cell lines. *Journal of Neuroscience* 1984; 4: 1453–1467.
44. Noronha-Blob L, Richard C, U'Prichard DC. Voltage-sensitive calcium channels in differentiated neuroblastoma × glioma hybrid (NG108-15) cells: characterization by quin 2 fluorescence. *Journal of Neurochemistry* 1988; **50**: 1381–1390.
45. Lambert DG, Willets JM, Atcheson R, Frost CL, Smart D, Rowbotham DJ, Smith G. Effects of propofol and thiopentone on potassium and carbachol evoked [^{3}H]noradrenaline release and increased $[Ca^{2+}]_i$ from SH-SY5Y human neuroblastoma cells. *Biochemical Pharmacology* 1996 (in press).

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Is inhibition of dopamine uptake relevant to the hypnotic action of i.v. anaesthetics?

H. KEITA, J. B. LECHARNY, D. HENZEL, J. M. DESMONTS AND J. MANTZ

Summary

We have examined the effects of ketamine, etomidate, propofol and thiopentone on the uptake of [^{3}H]-dopamine into rat striatal synaptosomes. [^{3}H]-dopamine uptake (5 min, 37 °C) was potently inhibited by nomifensine, a classical inhibitor of the dopamine carrier. All anaesthetics induced concentration-related inhibition of the uptake process, values for IC_{50} being 4.6×10^{-6}, 5.5×10^{-5}, 1.5×10^{-4} and 2.7×10^{-4} mol litre^{-1} for ketamine, etomidate, propofol and thiopentone, respectively. For all anaesthetics, inhibition of [^{3}H]-dopamine uptake was reversible with a non-competitive profile. These data suggest that inhibition of striatal dopamine uptake may represent a relevant target site for some, but not all, i.v. anaesthetics. (*Br. J. Anaesth.* 1996; **77**: 254–256)

Key words

Anaesthetics i.v., ketamine. Anaesthetics i.v., thiopentone. Anaesthetics i.v., etomidate. Anaesthetics i.v., propofol. Nerve, neurotransmitters.

There is a large body of evidence to suggest that enhancement of inhibitory (primarily $GABA_A$-mediated) or depression of excitatory (glutamate-mediated) neurotransmission, or both, may account for the dominant depressant effects of anaesthetics in the central nervous system. However, some experimental data suggest that other neuronal subpopulations, such as the striatal dopamine neurones, may contribute to some anaesthetic mechanisms. Indeed, an inverse correlation has been established between halothane anaesthetic requirements and the striatal dopamine content in mice [1]. Furthermore, striatal extracellular levels of dopamine or its metabolites were increased significantly during halothane anaesthesia in rats, which might be explained in part by block by volatile anaesthetics of the dopamine transporter [2].

The recent cloning of the DNA dopamine transporter gene in mammals has allowed extensive characterization of the pharmacology of this protein. Because of the hydrophobicity of the dopamine carrier, dopamine uptake may represent a target not only for volatile, but also for structurally heterogeneous i.v. anaesthetics. In support of this, ketamine and structurally related compounds have been shown to potently block dopamine uptake in the central nervous system [3]. Whether other i.v. anaesthetics can modulate the activity of the dopamine carrier remains to be determined. Therefore, the aim of this study was to examine the effects of i.v. anaesthetics on the uptake of dopamine into isolated, purified striatal nerve terminals (synaptosomes).

Materials and methods

Handling procedures, as written in the Guide for the Care and Use of Laboratory Animals, were followed throughout. Experiments were performed on male Sprague Dawley rats (Iffa-Credo, France) weighing 200–225 g and housed on a 12:12 light–dark cycle with food and water *ad libitum*. Animals were killed by stunning and decapitation, and striata removed rapidly from the brains and placed into ice cold sucrose 0.32 mol litre^{-1} containing EDTA 1 mmol litre^{-1}, dithiothreitol 0.25 mmol litre^{-1} and adjusted to pH 7.4. Synaptosomes were isolated and purified on a four-step Percoll gradient and diluted to protein 0.16 mg ml^{-1} with artificial cerebrospinal fluid (CSF) at 4 °C (mmol litre^{-1}): NaCl 126.5; $NaHCO_3$ 27.5; KCl 2.4; KH_2PO_4 0.5; $CaCl_2$ 1.1; $MgCl_2$ 0.83; Na_2SO_4 0.5; glucose 5.9; pargyline 10^{-2}; ascorbic acid 1; the pH was adjusted to 7.3 with a 95:5 v/v oxygen–carbon dioxide mixture.

Uptake was initiated by adding [2, 5, 6 ^{3}H]-dopamine (Amersham, England, 44 nmol litre^{-1}, 24 Ci mmol^{-1}, 1 mCi ml^{-1}) to the synaptosomal suspension at 37 °C. This was performed in either the absence of any pharmacological or anaesthetic agent (control), or both, or the presence of various concentrations of nomifensine 10^{-8}–5×10^{-5} mol litre^{-1} (Research Biochemical Incorporated, France) or ketamine (Sigma, USA) 10^{-6}–10^{-3} mol litre^{-1}, etomidate 10^{-6}–5×10^{-4} mol litre^{-1}, propofol 10^{-6}–5×10^{-4} mol litre^{-1} or thiopentone (Specia, France) 10^{-6}–10^{-3} mol litre^{-1}. Etomidate and propofol were dissolved in dimethylsulphoxide (Merck, Germany). After 5-min incubation, the mixture was vacuum filtered through glass filters (Whatman, GF/F, 0.70-µm retention capacity) and washed with 10 ml of ice-cold CSF. The radioactivity retained on the filters was extracted with NaOH 0.1 mol litre^{-1} and measured by liquid

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scintillation in Aquasol 2 (New England Nuclear, USA). Specific [^{3}H]-dopamine uptake was considered the difference between the radioactivity measured in both the presence and absence of nomifensine 10^{-5} mol litre^{-1}.

To determine if the effects of anaesthetics were not caused by irreversible synaptosomal damage, [^{3}H]-dopamine uptake was examined after removal of the anaesthetic from the buffer–synaptosomal suspension by vacuum and stirring rapidly for 30 min. Aliquots were removed at 15 and 30 min from an uptake mixture initially containing a concentration of anaesthetic corresponding to that inhibiting 50 % of specific high affinity [^{3}H]-dopamine uptake (IC_{50}), and [^{3}H]-dopamine uptake was determined as a function of the time that the mixture had been exposed to vacuum and stirring. Control experiments were also performed in parallel to allow comparison with anaesthetic-free mixtures exposed to the same conditions of vacuum and stirring.

To distinguish between competitive and non-competitive mechanisms of any observed inhibition of [^{3}H]-dopamine uptake by anaesthetics, the kinetics of anaesthetic-induced inhibition were investigated by incubating synaptosomes (37 °C, 5 min) with increasing concentrations [^{3}H]-dopamine (44–530 nmol litre^{-1}). The reaction was stopped by addition of ice-cold CSF followed by vacuum filtration, and the radioactivity retained on the filters was measured. The kinetic variables of the reaction (Vmax, K_m) were determined in the absence (control) and presence of a fixed concentration of anaesthetic corresponding to the IC_{50} value.

Concentration–response curves were generated by computer and IC_{50} values for inhibition of [^{3}H]-dopamine were calculated using the GraphPAD Software (San Diego, CA, USA). Results were considered reliable only if they had been reproduced in at least four independent experiments (each run in triplicate). Kinetic variables were analysed by ANOVA followed by the Student's t test corrected for the number of comparisons. $P < 0.05$ was considered the threshold for significance.

Results

Synaptosomal [^{3}H]-dopamine uptake increased with time and concentration and the mean value was 1.98 (SD 0.08) pmol litre/mg protein after 5 min incubation. It was potently blocked by nomifensine, a classical inhibitor of catecholamine uptake ($IC_{50} = 2.4 \times 10^{-7}$ mol litre^{-1}) (fig. 1). Non-specific uptake was always less than 5 % of the total radioactivity retained on the filters. The effects of ketamine, etomidate, propofol and thiopentone on [^{3}H]-dopamine uptake are displayed in figure 1.

For each anaesthetic tested, there was a concentration-related inhibition of the uptake of [^{3}H]-dopamine. Values for IC_{50} were 4.6×10^{-6}, 5.5×10^{-5}, 1.5×10^{-4} and 2.7×10^{-4} mol litre^{-1} for ketamine, etomidate, propofol and thiopentone, respectively. The 95 % confidence intervals were 7.6×10^{-7}–2.8×10^{-5} mol litre^{-1} for ketamine, 2×10^{-5}–10^{-4} mol litre^{-1} for etomidate, 5.6×10^{-5}–4×10^{-4} mol litre^{-1} for propofol and 2.3×10^{-5}–3.4×10^{-3} mol litre^{-1} for thiopentone. Dimethylsulphoxide did not affect [^{3}H]-dopamine uptake by itself.

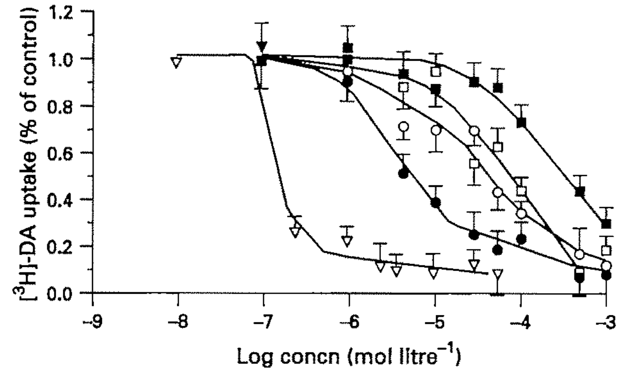

Figure 1 Inhibition of [^{3}H]-dopamine (DA) uptake by increasing concentrations of nomifensine (▽), ketamine (●), etomidate (○), propofol (□) and thiopentone (■). Data are mean, SD, and were obtained from at least four independent experiments.

Inhibition of the uptake process was totally reversible for each of the anaesthetics. Indeed, uptake of [^{3}H]-dopamine measured 15 and 30 min after removal of the anaesthetic from the solution was not significantly different from that observed in a time-dependent control. Dopamine uptake at 15 and 30 min after wash-out was mean 89 (SD 7) % and 94 (6) %, 84 (11) % and 96 (8) %, 87 (10) %, and 92 (9) %, 85 (9) % and 97 (6) % of control values for ketamine, etomidate, propofol and thiopentone, respectively.

All compounds exhibited a non-competitive profile, as assessed by both the lack of significant difference in K_m and the significant decrease in Vmax values observed between control experiments and those containing anaesthetics: Vmax (pmol/mg protein for 3 min) = 27 (6.1) for control, and 11 (2.8) ($P < 0.01$), 14 (3.4) ($P < 0.01$), 19 (4.1), ($P < 0.05$) and 21 (5.0) ($P < 0.05$) for ketamine, etomidate, propofol and thiopentone, respectively; K_m (nmol litre^{-1}) = 99 (18) for control, and 97 (19) (ns), 94 (18) (ns), 98 (16) (ns) and 101 (19) (ns) for ketamine, etomidate, propofol and thiopentone, respectively.

Discussion

We have shown that ketamine, etomidate, propofol and thiopentone inhibited the uptake of [^{3}H]dopamine in a reversible and non-competitive manner. The concentrations of ketamine and etomidate reported here are in agreement with those found in the plasma of anaesthetized humans, while those of propofol and thiopentone were likely to be outside the clinical range, even though such blood concentrations have been observed with propofol shortly after induction of anaesthesia [4]. Also, reversibility of effects is consistent with a clinically relevant action of i.v. anaesthetics on the dopamine carrier.

The anaesthetics exhibited a non-competitive profile of inhibition of [^{3}H]-dopamine uptake. Inhibition of dopamine uptake by isoflurane is non-competitive also and it exhibits no stereoselectivity [2]. Interestingly, not all transporters are relevant target sites for anaesthetic agents, as the striatal GABA carrier is also inhibited by some i.v. agents used at clinically relevant concentrations, while the glutamate transporter is not [5, 6]. For example, propofol exhibits more potent inhibitory effects on the GABA than on the dopamine carrier, whereas the opposite is true for ketamine [5] or other structurally related compounds such as phencyclidine [3]. Although the molecular mechanisms (direct effect on the carrier or actions via the lipid environment) whereby these anaesthetics block dopamine uptake remain to be elucidated, these results suggest that the anaesthetic carrier interactions exhibit some degree of specificity.

By increasing dopamine in the synaptic cleft, block of dopamine uptake may favour inhibitory neurotransmission, as stimulation of the striatal dopamine D2 postsynaptic receptors results in hyperpolarization. These results suggest that dopamine uptake might represent a target for some, but not all, i.v. anaesthetics.

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References

1. Segal IS, Walton JK, Irwin I, DeLanney LE, Ricaurte GA, Langston JW, Maze M. Modulating role of dopamine on anaesthetic requirements. *European Journal of Pharmacology* 1990; **186**: 9–15.
2. El-Maghrabi EA, Eckenhoff RG. Inhibition of dopamine transport in rat brain by volatile anesthetics. *Anesthesiology* 1993; **78**: 750–756.
3. Smith DJ, Azzaro AJ, Zaldivar SB, Palmer S, Lee HS. Properties of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. *Neuropharmacology* 1981; **20**: 391–396.
4. Servin F, Cockshott ID, Farinotti E, Haberer JP, Winckler C, Desmonts JM. Pharmacokinetics of propofol infusions in patients with cirrhosis. *British Journal of Anaesthesia* 1990; **65**: 177–183.
5. Mantz J, Lecharny JB, Laudenbach V, Henzel D, Peytavin G, Desmonts JM. Anaesthetics affect the uptake, but not the depolarization-evoked release of GABA in rat striatal synaptosomes. *Anesthesiology* 1995; **82**: 502–511.
6. Nicol B, Rowbotham, Lambert DG. Glutamate uptake is not a major target site for anaesthetic agents. *British Journal of Anaesthesia* 1995; **75**: 61–65.

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Myocardial extraction of bupivacaine in anaesthetized sheep and by hearts of sheep and rats *in vitro*

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Summary

We observed the *in vivo* kinetics of bupivacaine in the cardiopulmonary system, particularly in the pulmonary artery, the upper part of the descending aorta and the coronary sinus of anaesthetized sheep, each of which received a high dose infusion into the central vein. In some experiments dilution curves were monitored for the non-extracted dye, indocyanine green. Concentrations of bupivacaine were approximately 20% lower in the aorta than in the pulmonary artery. This gradient of bupivacaine was present across the lung for 5–10 min. Concentrations of bupivacaine in the coronary venous plasma were also markedly lower than at the arterial site. Initially more than 50% of the amount of bupivacaine at the arterial site was removed by the heart. Later, the myocardial extraction ratio decreased and plateaued at a value of 0.30–0.40. At this time, concentrations of bupivacaine in the pulmonary artery were approximately 12 μg ml^{-1}. Therefore, approximately 0.3–0.6 mg of bupivacaine were extracted per minute by the sheep heart *in vivo*. On the other hand, isolated perfused rat hearts did not substantially remove bupivacaine (2 μg ml^{-1}) from the medium. Approximately one-third of ^{14}C-bupivacaine was retained in slices of rat and sheep myocardial tissue. However, there was no evidence that metabolism played a substantial role in the cardiac kinetics of bupivacaine. (*Br. J. Anaesth.* 1996; **77**: 257–264)

Key words

Anaesthetics local, bupivacaine. Liver, metabolism. Pharmacokinetics, bupivacaine. Rat. Sheep. Model, rat. Heart, isolated preparation. Lung.

Amide-linked local anaesthetic drugs, such as bupivacaine, mepivacaine or prilocaine, are used widely for regional anaesthesia. Usually these drugs are injected extradurally at relatively high doses. Almost the whole amount of drug enters the circulation because the rate of degradation at the site of injection is negligible [1, 2]. Accordingly, these drugs reach relatively high concentrations in plasma which are close to those at which toxic effects are likely to occur [3, 4].

Adverse effects in the central nervous system, such as convulsions, may occur at concentrations which are 2–4-fold higher than those which are observed in the course of regional anaesthesia. On the other hand, cardiovascular functions are affected at higher concentrations than those which cause side effects in the central nervous system. The ratio between clinically effective doses and those producing non-fatal toxicity are not substantially different between commonly used local anaesthetics. However, cardiotoxic events with a fatal outcome appear to be associated with bupivacaine in particular [5, 6]. This feature of bupivacaine may be explained partly by pharmacokinetic properties such as disposition in the myocardial tissue.

In this study we monitored concentrations of bupivacaine *in vivo* in the cardiopulmonary system, that is in the pulmonary artery, upper part of the descending aorta and coronary sinus. Bupivacaine was infused into the central vein at a relatively high infusion rate. *In vitro* experiments using perfused rat hearts or sliced myocardial tissue of rats and sheep were performed in order to determine if metabolism is important for the cardiopulmonary kinetics of bupivacaine.

Materials and methods

EXPERIMENTS ON SHEEP *IN VIVO*

The experiments were approved by the appropriate governmental committee according to the Animal Protection Law. Adult sheep (body weight 45–97 kg) were anaesthetized with a continuous infusion of midazolam 0.25 mg kg^{-1} min^{-1} and buprenorphine 0.01 mg kg^{-1} min^{-1}. The trachea was intubated and the lungs ventilated artificially with 70% nitrous oxide in oxygen. A 7-French gauge cannula was inserted into the right atrium via the right jugular vein and into the upper part of the descending aorta via the femoral artery. The correct position of all catheters was verified by x-ray. A Morawitz cannula was inserted into the right jugular vein and positioned in the ostium of the coronary sinus where it was blocked to avoid mixed sampling of central venous and coronary venous blood. The tip of this cannula was directed 1 cm into the coronary sinus. The hemiazygos vein, which in sheep drains into the coronary sinus, was blocked by a Fogarty catheter. Blood from the coronary sinus (60–80 ml min^{-1}/100 g left ventricle) was directed into an external

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Table 1 Description of the experimental design of the pharmacokinetic studies in sheep. [a]Pharmacokinetic data of short-lived experimental drugs were determined during the first experiment; each sheep received Urografin x-ray contrast medium to see if the catheters were placed correctly; [b]hind leg; [c]mild acidosis for 30 min; [d]RR_{art} = mean arterial pressure, HR = heart rate, HMV = heart minute volume

				Haemodynamic data[d] first experimental period						
ID No.	Weight (kg)	Sex (M/F)	First drug	Pre-RR_{art}	HR	HMV	Post-RR_{art}	HR	HMV	Second drug
118	48.0	F	Untreated control	98	68	5.8	90	73	5.5	Bupivacaine
149	55.0	F	Local hyperthermia[b]	103	98	4.8	107	97	5.1	Bupivacaine
168	85.0	F	CO_2 and lactate acidosis[c]	102	64	8.9	104	68	8.0	Bupivacaine
108	44.5	F	SHU 508	95	83	7.6	100	80	8.1	Bupivacaine
120	55.5	F	SHU 508	119	68	6.3	115	66	6.8	Bupivacaine
141	51.0	F	R 80122	114	76	7.3	118	83	7.8	Bupivacaine
169	76.0	F	R 80122	137	80	8.9	141	77	8.2	Bupivacaine
171	85.0	F	R 80122	130	70	5.8	141	74	5.7	Lignocaine
172	97.0	F	R 80122	119	80	6.9	125	74	6.8	Lignocaine
192	70.0	M	Organic nitrate, papaverine intracoronary	132	63	4.2	132	62	4.3	Prilocaine

electromagnetic flow probe (501 D, Carolina Medical Electronics, Inc. King, NC, USA) and directed back from the extracorporeal catheter into the left jugular vein via a shunt (for further details see [7]). A thermodilution Swan-Ganz catheter (F7, Arrow Int. Reading, PA, USA) was inserted. Pulmonary arterial blood was obtained from a sampling port of this catheter. Cardiac output was measured by the thermodilution technique (BN 6560, August Fischer KG, Goettingen, Germany). At least two measurements were made and the mean value recorded. Additionally, other variables such as arterial pressure and electrocardiogram, plasma electrolyte, oxygen and lactate concentrations were recorded.

The experiments were scheduled originally for studies on the intravascular distribution and pharmacodynamic properties of investigational drugs (see table 1), such as spontaneously degrading ultrasonic bubbles (experiments 108, 120) or inhibitors of phosphodiesterases (experiments 141, 169, 171, 172). The ultrasonic bubbles SHU 508 are very short-lived because of their physicochemical instability and the inhibitor of phosphodiesterase, R80122, exhibits its pharmacodynamic action only for a short period of time. Flow measurements (Doppler sonography) were performed in experiment 192 after intra-coronary administration of organic nitrate and papaverine. Other experiments were performed to obtain reference values in controls (118) and in animals after transient mild hyperthermia of the hind limb (experiment 149), or after transient lactate acidosis (experiment 168). Therefore, these animals received no investigational drugs before bupivacaine. When haemodynamic and other major clinical variables returned to stable baseline values, racemic bupivacaine, was infused into a catheter introduced into the central vein at a rate of 0.2 mg kg^{-1} min^{-1}. The tip of this tubing was positioned near the right atrium. In two experiments another infusion regimen was used: one sheep (experiment 108) received 0.05, 0.1, 0.2 and 0.4 mg kg^{-1} min^{-1} each for 10 min. Another animal was dosed with 0.1 mg kg^{-1} min^{-1} for 0–30 min and 0.2 mg kg^{-1} min^{-1} for 30–45 min (experiment 118). In experiment 108, death occurred when the highest dose was administered. The other experiments were terminated by injection of potassium chloride.

In some experiments (149, 168, 169 and 186) indocyanine green (ICG) 0.05 mg kg^{-1} min^{-1} (approximately 80 mg Cardiogreen, Paesel, Frankfurt, FRG) was infused concomitantly with bupivacaine into the central vein just before the right atrium. Blood samples (5 ml) were obtained from the pulmonary artery, descending aorta and coronary sinus 1, 2, 5, 7, 10, 15, 20, 25 and 30 min after the start of infusion. Between the site of infusion and the first site of blood sampling, blood passed through the right atrium and ventricle. The plasma fraction was stored at −20 °C until analysis by HPLC.

IN VITRO EXPERIMENTS

Isolated rat hearts were obtained from male Wistar rats during urethane anaesthesia. The organs were prepared according to the Langendorff technique and were connected to the perfusion apparatus (Langendorff apparatus modified according to Schuler, Hugo Sachs Elektronik KG, March, Germany). The experiments were performed without an external pacemaker. The isolated rat hearts were perfused with oxygenated Krebs–Ringer–bicarbonate buffer supplemented with D-glucose 2 mg ml^{-1} at a constant pressure of 52.5 mm Hg. Sham perfusions were performed under identical conditions but without insertion of a rat heart.

Sheep myocardial tissue was obtained from a local slaughterhouse. When the trachea-lung-heart system was removed from the animal, a 5–10-g specimen of the ventricle was obtained immediately and transferred into ice-cold saline solution containing heparin 20 I.E. ml^{-1}. Incubations of tissue slices were started approximately 1 h after the animal had been killed. Rat hearts were obtained from untreated male Wistar rats after neck dislocation and bleeding via an incision of the jugular vein. Slices of rat and sheep hearts of 0.5 mm thickness (0.2 g wet tissue/ml) were incubated in Krebs–Ringer–bicarbonate buffer or phosphate buffer (66 mmol litre^{-1} pH 7.4) supplemented with bovine serum albumin 15 mg or D-glucose 1 mg ml^{-1}. The tissue–buffer solutions (5–6 ml) were incubated with ^{14}C-bupivacaine (gift from Astra, Södertalje, Sweden) 0.3 (rat) or 2 (sheep) µg ml^{-1} in 25-ml Erlenmeyer vials under a continuous stream of carbogen. Ten samples, each 200 µl, were taken from the medium and stored at −20 °C until analysis by thin layer chromatography (TLC).

ANALYSIS

ICG kinetics were recorded spectrophotometrically in plasma samples using an Eppendorf photometer 2116 at a wavelength of 623 nm. Unlabelled bupivacaine was quantified by non-enantioselective HPLC, as described previously [8]. Briefly, the samples were spiked with internal standards (mepivacaine or pentacaine) and extracted with n-hexane under alkaline conditions. The organic extract was re-extracted into 100 µl of 50 % H_3PO_4 0.2 mol litre^{-1}–50 % n-hexane. A fraction of the acid layer (20 or 50 µl) was injected onto a 5-µm NC phenyl-hypersil analytical column (Bischoff, Nettetal, FRG). HPLC was run at 1 ml min^{-1} using a mobile phase of 60 % acetronitrile–40 % H_3PO_4 0.01 mol litre^{-1}, pH 3.3. UV absorbance was monitored at 214 nm. The analytical limit of detection was approximately 10 ng ml^{-1} for a 200-µl sample. The variation of results for repeated analysis of low concentrations was 1.5–4.8 % (inter-day) and 1.1–3.7 % (intra-day).

^{14}C-labelled bupivacaine was extracted from the samples, as described above, with the exception that either n-hexane or dichloromethane was used. Bupivacaine and ^{14}C-labelled products were separated on silica gel-coated plastic sheets by TLC in chloroform–methanol–triethylamine 20:1:0.1 (v/v/v). The lanes were scanned by a TLC linear analyser LB 2842 (Berthold, Wildbad, FRG). Also, HPLC was applied to see if metabolites had been formed.

CALCULATIONS AND STATISTICS

Pulmonary and cardiac extraction ratios were calculated from the concentration in the inflow, C_{in}, that is pulmonary–arterial or arterial plasma, and the outflow, C_{out}, that is arterial or coronary venous plasma, by

$$(C_{in} - C_{out})/C_{in}$$

The pharmacokinetic variables of bupivacaine elimination by isolated rat hearts, such as elimination half life ($T_{\frac{1}{2}}$) and steady state volume of distribution (V^{ss}) were calculated from the concentration *vs* time curve using a standard two-compartmental model assuming first-order elimination kinetics, as described previously [9]. The elimination rate constant (k_{el}) was determined by linear regression analysis from the semi-logarithmic concentration *vs* time curve and volume of distribution was calculated from dose/C_{β}, the intercept of the second part of the semi-logarithmic concentration *vs* time curve extrapolated to time 0.

Results are given as arithmetic mean (SEM) or geometric mean (SEM), where indicated. Statistical analysis was performed either by a two-sided unpaired *t* test or by a paired *t* test (comparison of C_{in} and C_{out}).

Results

EXPERIMENTS *IN VIVO*

Adult sheep ($n = 10$) were scheduled originally for experiments on pharmacokinetic and pharmacodynamic properties of investigational drugs, such as enhancers of the ultrasonic signal and phosphodiesterase inhibitors, or some experiments served as controls; when all variables had returned to baseline values a relatively high dose of bupivacaine 0.2 mg kg^{-1} min^{-1} was infused into the central vein just before the right atrium for 30 min. Two sheep were studied at other infusion rates (see materials and methods).

The time courses of plasma concentrations of bupivacaine in the pulmonary artery, upper part of the descending aorta and coronary sinus are shown in figure 1. At the end of infusion, plasma concentrations were approximately 11 µg ml^{-1} in the pulmonary artery and in the descending aorta (see tables 3, 4). Although these concentrations are relatively high, impairment of cardiac functions was not

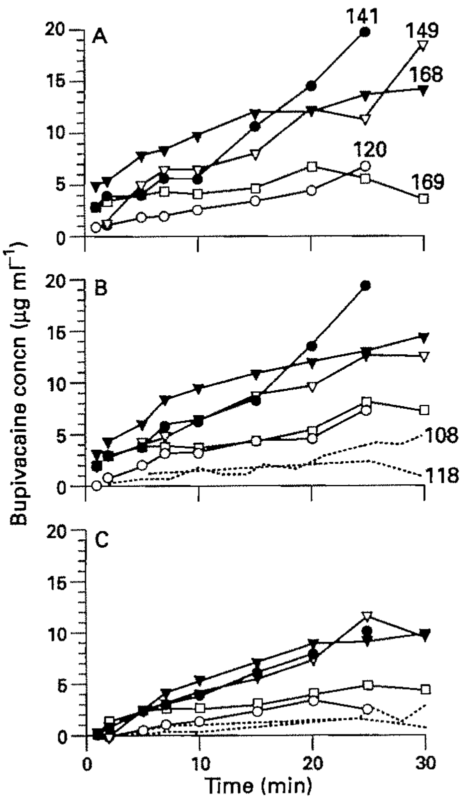

Figure 1 Concentrations of bupivacaine in the plasma of the pulmonary artery (A), upper part of the descending aorta (B) and coronary sinus (C) in anaesthetized female sheep. Bupivacaine was infused into the central vein at a rate of 0.2 mg kg^{-1} min^{-1} over 30 min. The curves depict results from individual experiments. The curves without symbols refer to two pilot experiments where bupivacaine was administered using different rates of infusion.

Table 2 Haemodynamic variables for sheep during infusion of bupivacaine (B), lignocaine (L) or prilocaine (P). Concn = Concentration in the last arterial plasma sample; RR = mean arterial pressure (mm Hg), HR = heart rate (beat min^{-1}), HMV = heart minute volume (litre) (first column = before start of all experiments)

ID No.	Infusion rate ($\text{mg kg}^{-1}\ \text{min}^{-1}$)	Concn ($\mu\text{g min}^{-1}$)	RR HR HMV	Time (min) 0	5	10	15	20	25	30
118	0.1	4.2	98	90	89	90	86	86	94	90
(B)			68	73	76	71	75	73	73	75
			5.8	5.5	5.3	5.6	5.6	5.6	5.7	5.6
149	0.2	12.3	103	107	108	110	103	104	103	108
(B)			98	97	94	102	96	94	94	96
			4.8	5.1	4.8	5.3	5.1	4.9	4.9	5.1
168	0.2	14.1	102	104	106	100	103	107	101	99
(B)			64	68	70	67	65	65	66	67
			8.9	8.0	8.0	8.4	8.0	7.9	7.7	8.1
108	0.05, 0.1,	4.6	95	100	97	95	101	99	99	101
(B)	0.2, 0.4		83	80	84	83	83	79	79	82
	10 min each		7.6	8.1	8.3	8.2	7.7	8.0	8.3	7.8
120	0.2	7.1	119	115	113	117	110	113	113	113
(B)			68	66	68	64	63	66	68	63
			6.3	6.8	7.1	6.6	7.0	6.7	6.7	6.9
141	0.2	19.0	114	118	118	116	113	122	113	112
(B)			76	83	86	82	85	81	87	84
			7.3	7.8	7.4	7.4	8.0	7.6	7.7	7.7
169	0.2	7.1	137	141	147	146	141	137	137	143
(B)			80	77	80	78	73	80	77	78
			8.9	8.2	8.3	8.3	8.4	8.5	8.6	8.1
171	0.2	7.1	130	141	137	137	142	140	138	141
(L)			70	74	71	73	77	75	75	71
			5.8	5.7	5.8	5.6	5.7	5.6	5.5	5.7
172	0.2	6.9	119	125	131	120	122	129	124	126
(L)			80	74	75	71	72	75	76	72
			6.9	6.8	6.8	7.1	6.8	6.6	7.0	6.8
192	0.2	10.1	132	132	136	127	130	138	135	136
(P)			63	62	64	63	61	64	62	65
			4.4	4.3	4.4	4.2	4.5	4.5	4.4	4.4

induced except in experiment 108 (dose-finding experiment) where fatal cardiac failure was intended. Cardiac arrest occurred 5 min after setting the infusion rate to 0.4 $\text{mg kg}^{-1}\ \text{min}^{-1}$. In other cases, vascular resistance of coronary vessels was increased, which indicates that bupivacaine may affect myocardial perfusion under certain circumstances. All other variables, such as arterial pressure, heart rate, stroke volume and vascular resistance, were not markedly impaired (see table 2).

Shortly after the start of infusion the concentration of bupivacaine in plasma samples from the descending aorta was lower than the corresponding value in the pulmonary artery. Thus there was a gradient of bupivacaine concentration across the lung which lasted 5–10 min. In contrast, concentrations of indocyanine green were almost identical in these samples which indicates that only bupivacaine was retained by the lung. The fraction of pulmonary extracted bupivacaine was calculated from concentrations in paired samples from the aorta and pulmonary artery. The results are shown in the lower panel of figure 2 and table 3. Approximately 10 min after starting the infusion, bupivacaine concentrations were almost identical in blood samples obtained before and after the lung, thereby indicating that bupivacaine was extracted by the lung only for a short time.

In our study we have obtained evidence that myocardial tissue may also be an important compartment for the distribution of bupivacaine. Samples from the coronary venous outflow contained

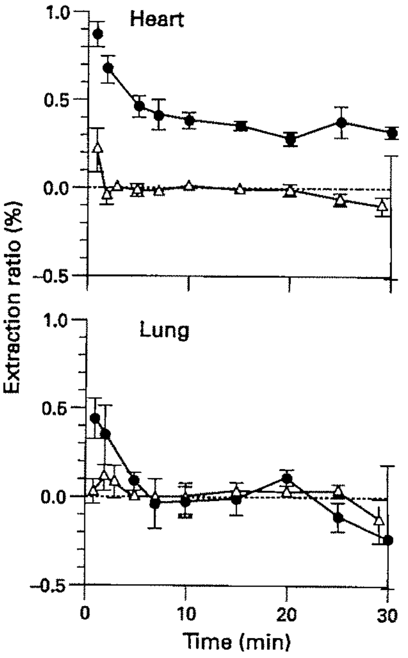

Figure 2 Extraction of bupivacaine by the heart and lung of anaesthetized sheep. Myocardial and pulmonary extraction ratios $((C_{\text{in}} - C_{\text{out}})/C_{\text{in}})$ of bupivacaine (●) and indocyanine green (ICG) (○) in female sheep are given as arithmetic mean, SEM ($n = 5$). ICG was infused concomitantly to bupivacaine in three experiments (149, 168, 169) and in one additional experiment (186) without administration of local anaesthetic.

Table 3 Concentration gradient of local anaesthetics across the lung and heart in adult sheep *in vivo*. Results of individual experiments are shown; rate of infusion 0.2 mg kg^{-1} min^{-1} for 30 min with the exception of *108, 118 (see table 2 and Materials and methods for details). B = bupivacaine, L = lignocaine, P = prilocaine. [a]Concentration below limit of detection; [b]No sample available; [c]Sample obtained at 40 min.

	Time (min)								
	2 $(C_{in}-C_{out})/C_{in}$	5	10	15	20	25	30	Last sample	C_{pa} (μg ml^{-1})
Lung									
118 (B)*	b	b	b	b	b	b	b		b
149 (B)	(1.00)[a]	0.17	0.07	−0.10	0.22	−0.12	0.32		18.2
168 (B)	0.22	0.23	0.04	0.10	0.02	0.05	0.00		14.1
108 (B)*	b	b	b	b	b	b	b		b
120 (B)	0.21	−0.06	0.26	−0.30	0.02	−0.09	b		6.5
141 (B)	0.25	0.12	−0.14	−0.22	0.07	−0.03	b		19.6
169 (B)	0.14	0.02	0.13	0.05	0.23	−0.41	−1.02		3.5
171 (L)	0.28	0.12	−0.28	0.08	−0.31	0.17	−1.42		3.2
172 (L)	0.10	0.09	−0.38	−0.15	0.02	−0.35	−1.29		3.0
192 (P)	b	b	b	b	b	b	b		b
Heart									C_a (μg ml^{-1})
118 (B)*	b	0.26	0.23	0.13	0.28	0.35	b	0.27[c]	4.2
149 (B)	(1.00)[a]	0.39	0.30	0.38	0.23	0.10	0.24		12.3
168 (B)	0.80	0.52	0.42	0.33	0.26	0.30	0.31		14.1
108 (B)*	0.73	0.58	0.67	0.36	0.34	0.48	0.43		4.6
120 (B)	0.81	0.65	0.57	0.45	0.23	0.63	b		7.1
141 (B)	0.61	0.35	0.37	0.27	0.42	0.49	b		19.0
169 (B)	0.47	0.37	0.26	0.31	0.24	0.38	0.39		7.1
171 (L)	0.89	0.59	0.45	0.39	0.22	0.25	0.31		7.1
172 (L)	(1.00)[a]	0.14	0.06	−0.13	0.25	0.18	0.31		6.9
192 (P)	0.85	0.79	0.11	0.14	0.15	0.50	0.20		10.1

Table 4 Myocardial disposition of bupivacaine and lignocaine in female sheep. Values are arithmetic mean (SE) (individual results are shown in fig. 1) or mean of two experiments. [a]Experiments performed at an infusion rate of 0.2 mg kg^{-1} min^{-1} (except 108, 118). b = below limit of detection. Extraction ratio = $(C_a - C_{cv}) \times 100$; rate of uptake = $(C_a - C_{cv}) \times$ coronary blood flow. *$P < 0.05$ C_{in} *vs* C_{out} (paired *t* test)

	Time (min)						
	2	5	10	15	20	25	30
Bupivacaine ($n = 5$)[a]							
C_a (μg ml^{-1})	2.3 (0.8)	4.0 (0.6)	5.7 (1.1)	7.3 (1.3)	8.8 (1.8)	11.8 (2.1)	11.2 (1.6)
C_{cv} (μg ml^{-1})	0.8 (0.3)*	2.2 (0.4)*	3.6 (0.7)*	4.8 (0.9)*	6.2 (1.1)*	7.5 (1.6)*	7.8 (1.3)*
Extraction ratio (%)	67 (8)	46 (6)	38 (5)	35 (4)	28 (4)	38 (9)	32 (4)
Rate of uptake (mg min^{-1}) (mg min^{-1})	0.28 (0.08)	0.26 (0.05)	0.33 (0.07)	0.37 (0.06)	0.39 (0.12)	0.65 (0.20)	0.51 (0.08)
Lignocaine ($n = 2$)							
C_{in} (μg ml)	3.0; 3.0	6.4; 4.3	5.3; 5.8	7.6; 5.3	7.0; 6.0	6.7; 6.5	7.8; 6.9
C_{out} (μg ml)	0.3; b	2.6; 3.7	2.9; 5.4	4.7; 5.9	5.4; 4.5	5.0; 5.4	5.4; 4.8
Extraction	95	37	26	13	24	22	31
Rate of uptake (mg min^{-1})	0.42	0.51	0.21	0.17	0.23	0.21	0.34

much less bupivacaine than corresponding samples from the arterial site of circulation (fig. 1, tables 3, 4). Immediately after the start of infusion the arteriovenous difference of bupivacaine concentration across the heart reached almost 80 % of the level at the arterial site (fig. 2). Afterwards the gradient of bupivacaine concentration decreased and finally plateaued at approximately 30–40 %. On the other hand, indocyanine green was present in these samples in almost identical concentrations. Thus it must be assumed that bupivacaine was subjected to substantial first-pass extraction by sheep hearts *in vivo*. Other experiments with indocyanine green but without bupivacaine confirmed that the kinetics of indocyanine green which were monitored on-line with a fibreoptic system, were not different at our sampling sites (results not shown).

Similar results concerning myocardial extraction of drugs were obtained in experiments 171, 172 and 192 where other local anaesthetics, lignocaine and prilocaine, were used (see table 3). The extraction ratios of lignocaine and prilocaine appeared to be lower compared with bupivacaine. However, further studies are needed to assess if the rate of myocardial extraction is different for these local anaesthetic drugs.

It is unlikely that the experiments performed before infusion of these drugs substantially affected

Table 5 Kinetics of bupivacaine in isolated perfused rat heart. Values are arithmetic mean (SEM). The perfusion experiments were carried out in a Langendorff perfusion apparatus using bupivacaine 2 μg ml^{-1}. $C_p$max = Highest observed plasma concentration after reaching equilibrium; $C_p$end = concentration at end of experiments. $T_{\frac{1}{2}}$ = elimination half-life; V^{ss} = volume of initial distribution, calculated from the dose and the intercept of the second part of the semi-logarithmic concentration *vs* time curve extrapolated to time 0

	Perfused heart ($n = 9$)	Sham perfusion ($n = 5$)
$C_p$max (μg ml^{-1})	2.1 (0.1)	1.9 (0.1)
$C_p$end (μg ml^{-1})	1.8 (0.1)	1.9 (0.1)
$T_{\frac{1}{2}}$ (min)	647 (44)	1482 (222)
V^{ss} (ml)	49.2 (1.7)	51.1 (1.9)

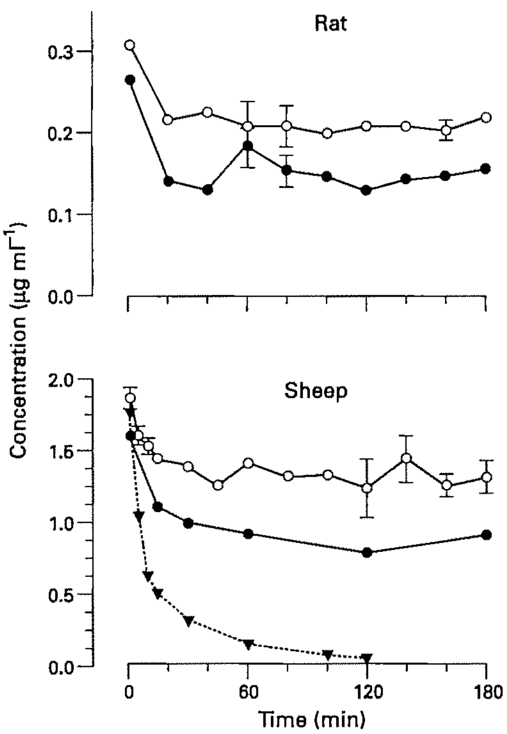

Figure 3 Time course of bupivacaine (●) and total radioactivity (○) in the medium of incubated slices of myocardial tissue. Slices of rat ($n = 5$) and sheep ($n = 4$) hearts were incubated *in vitro* (0.2 g organ/ml) with ^{14}C-labelled bupivacaine 0.3 or 2 μg ml^{-1}. The results of a single experiment with sheep liver slices are included (▼ = bupivacaine).

the pharmacokinetic fate of bupivacaine, lignocaine or prilocaine. All experiments showed almost the same effect, although the animals underwent a very different programme and some served as controls.

EXPERIMENTS *IN VITRO*

In order to evaluate if substantial cardiac extraction of bupivacaine can also be confirmed *in vitro* using organs from small laboratory animals, we studied the kinetics of bupivacaine in the Langendorff preparation of isolated rat hearts. Bupivacaine was administered to the isolated organs in an initial concentration of 2 μg ml^{-1} which corresponds to a dose of approximately 100 μg/g of organ. The time course of bupivacaine concentrations in the medium of isolated perfused rat hearts was almost identical to the reference curve of sham perfusions (table 5). The latter experiments were carried out using the same Langendorff perfusion apparatus but without the isolated organ in order to examine the influence of spontaneous hydrolysis and absorption by the tubing material.

Slices of rat or sheep hearts were incubated with ^{14}C-labelled bupivacaine 0.3 (rat) or 2 (sheep) μg ml^{-1} *in vitro*. Under these circumstances the total load was approximately 1.5 or 10 μg of drug/g of organ. The concentration of bupivacaine in the medium decreased substantially during the first 30 min of incubation which indicates that this compound was bound to tissue proteins (see fig. 3). This tissue-bound fraction accounted for approximately 30–50 % of the total amount of bupivacaine. However, we did not obtain convincing evidence that slices of myocardial tissue of rats or sheep metabolized bupivacaine *in vitro*. In contrast with sheep hearts, slices of sheep liver metabolized ^{14}C-bupivacaine very effectively *in vitro* (see fig. 3, results of a single experiment are shown).

Discussion

Under normal clinical conditions, maximum plasma concentrations of amide-linked local anaesthetics are relatively close to the margin of safety with respect to toxicity [1, 3, 5, 10–12]. Although it is generally believed that the therapeutic index is not substantially different between lignocaine, mepivacaine, prilocaine and bupivacaine, it has been suggested that bupivacaine in particular may be associated with serious cardiac toxicity [5, 6]. In particular, appropriate observations were reported when highly concentrated solutions of bupivacaine had been used. If it is true that the side effects of bupivacaine carry a higher cardiotoxic risk compared with other compounds, this effect may be partly explained by the pharmacokinetic features of this compound, that is a high degree of protein binding and persistence within the tissue because of its long elimination half-life. Our experiments were undertaken in order to evaluate the disposition of bupivacaine in the cardiopulmonary system of sheep *in vivo*.

We achieved relatively high systemic concentrations of bupivacaine in anaesthetized sheep undergoing artificial ventilation. These concentrations exceeded the values of acutely toxic concentrations reported from other studies [6]. However, cardiac functions (stroke volume, arterial pressure, ECG) were not seriously impaired in most of our experiments.

For a short period of time we measured an "arteriovenous" gradient of bupivacaine concentration across the lung. The difference in concentration was highest immediately after the start of infusion and was decreased to almost 0 within 15 min. Thus it may be assumed that initially considerable amounts of bupivacaine were removed from the blood during its passage through the lung. However, this filtering effect of the lung was only short-lived. Similar observations were made for bupivacaine and prilocaine in isolated perfused lungs of rabbits and rats [13–15]. This feature of sheep lung concerning the kinetics of bupivacaine is similar to our findings in a clinical study in patients undergoing extradural anaesthesia [16]. It is likely that pulmonary first-pass extraction of bupivacaine is caused mainly by binding to tissue proteins and that this process is limited by the capacity of binding. It must be assumed that the rate of metabolic elimination of local anaesthetics by the lung is very small. Accordingly, most of the extracted drug is released by the lung into the blood stream and is finally degraded by metabolism at extrapulmonary sites.

The gradient of bupivacaine concentrations between arterial and coronary venous plasma indicates that the sheep heart may have a substantial influence on the pharmacokinetic effect of bupivacaine. This cardiac filter effect was relatively high immediately after the start of infusion. Within the following 10 min the difference in bupivacaine concentration across the heart decreased to approximately 50% of initial values. This might be caused by capacity-limited binding to the tissue. However, afterwards the cardiac extraction ratio of bupivacaine plateaued at approximately 30–40% of the amount which is present in the arterial inflow. This kinetic feature of bupivacaine, verified in the sheep heart, is remarkable, particularly as the ratio remained stable although systemic concentrations of bupivacaine still increased.

We cannot fully exclude the fact that the experimental design before infusion of bupivacaine may have interacted with the disposition of bupivacaine in the cardiopulmonary system. However, we do not believe that these substrates substantially affected the kinetics of bupivacaine for the following reasons: all important variables had returned to baseline levels when bupivacaine was administered. In some experiments only short-lived ultrasonic bubbles were injected, which are small vesicles prepared from galactose and filled with air. These compounds had been completely degraded before bupivacaine was infused. Other animals received inhibitors of phosphodiesterase which are pharmacologically active only for a short time. For both types of experiments each animal served as its own reference in order to compare different dosing rates or different injection sites with each other. This design has been accepted by others [17, 18]. Other experiments were undertaken in order to obtain reference values for haemodynamic variables in untreated controls or in animals which underwent mild local hyperthermia or short-term acidosis induced by carbon dioxide or lactate. Therefore, our results were obtained in three different groups of "second-hand" animals which received (a) investigational drugs, (b) local hyperthermia or acidosis for a short time or (c) were untreated controls. Therefore, we believe that these different categories of basic experiments did not have a substantial influence on the kinetics of bupivacaine as we obtained almost the same results for all animals.

We cannot definitively answer the question of whether or not other amide-linked local anaesthetics undergo high cardiac extraction in sheep. Nevertheless, from the results of the two experiments where lignocaine was used, we would expect that cardiac extraction of lignocaine does occur. However, it might be considerably lower than that of bupivacaine. Contrary to our results in sheep, elimination of bupivacaine by perfused rat hearts was negligible. The time course of bupivacaine concentrations in the medium of isolated hearts was almost identical to the course obtained for sham perfusions. The elimination half-lives largely exceeded the perfusion time in both cases. Therefore the differences between the elimination half-lives of bupivacaine in isolated hearts and those in sham controls are not important.

In contrast, bupivacaine was bound substantially to the incubated myocardial tissue of rats and sheep. However, only approximately 0.5–4 µg of ^{14}C-labelled bupivacaine was retained per gram of sliced myocardial tissue *in vitro*. This is much less than the amount which is removed by sheep hearts *in vivo*. Altogether, neither rat hearts nor sheep hearts exhibited substantial metabolism of bupivacaine *in vitro*.

In conclusion, the risk of bupivacaine in inducing fatal cardiotoxicity may be related to the pharmacokinetic properties of this compound. Bupivacaine is taken up from the blood stream by sheep hearts at a large fraction of 0.3–0.4, even at high plasma concentrations. The driving force by which bupivacaine is removed by the myocardial tissue of sheep *in vivo* was unclear until now. From the results of our *in vitro* experiments we suggest that metabolism is not important, but that binding to the tissue is a main process leading to first-pass extraction of bupivacaine. However, it is unlikely that this effect fully explains how the concentration differences are established between the aorta and coronary sinus, because the extraction ratio remained high for a long time (at lest 30 min) although bupivacaine was infused continuously and the drug load to the myocardial tissue was thus increasing. Another explanation is that bupivacaine may be drained substantially by the lymph flow of hearts because this drug is highly lipophilic and cardiac lymph flow is an important process for the myocardial tissue. But if this were true, we would expect that this effect should also be detected in the lung.

Acknowledgements

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References

1. Burm AL, Vermeulen NPE, van Kleef JW, de Boer AG, Spierdijk J, Breimer DD. Pharmacokinetics of lignocaine and bupivacaine in surgical patients after extradural administration—simultaneous investigation of absorption and disposition kinetics using stable isotopes. *Clinical Pharmacokinetics* 1987; 13: 191–203.
2. Burm AGL. Clinical pharmacokinetics of extradural and spinal anaesthesia. *Clinical Pharmacokinetics* 1989; **16**: 283–311.
3. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; 58: 717–731.
4. Tucker GT, Mather LE. Properties, absorption and disposition of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia: Lippincott, 1988; 47–110.

5. Reiz S, Nath S. Cardiotoxicity of local anesthetic agents. *Anesthesiology* 1986; **58**: 736–746.
6. Nancarrow C, Rutten AJ, Runciman WB, Mather LE, Carapetis RJ, McLean CF, Hipkins SF. Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine, and ropivacaine in the sheep. *Anesthesia and Analgesia* 1989; **69**: 276–283.
7. Hering JP, Schröder, T, Singer, D, Hellige G. Influence of pH-management on hemodynamics and metabolism in moderate hypothermia. *Journal of Thoracic and Cardiovascular Surgery* 1992; **104**: 1388–1395.
8. Michaelis HC, Geng W, Kahl GF, Foth H. Sensitive determination of bupivacaine in human plasma by high-performance liquid chromatography. *Journal of Chromatography* 1990; **527**: 201–207.
9. Gibaldi M. Noncompartmental pharmacokinetics. In: Gibaldi M, ed. *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd Edn. Philadelphia: Lea & Febinger, 1984; 17–29.
10. Moore DC, Crawford RD, Scurlock JE. Severe hypoxia and acidosis after local anesthetic-induced convulsions. *Anesthesiology* 1980; **52**: 259–260.
11. Scott, DB. Toxic effects of local anaesthetic agents on the central nervous system. *British Journal of Anaesthesia* 1986; **58**: 732–735.
12. Fujita Y. Comparative direct effects of lidocaine and bupivacaine on regional myocardial function in dogs at non-cardiovascular toxic levels. *Anesthesia and Analgesia* 1994; **78**: 1158–1163.
13. Palazzo MGA, Kalso EA, Argiras E, Madgwick R, Sear JW. First pass lung uptake of bupivacaine: Effect of acidosis in an intact rabbit lung model. *British Journal of Anaesthesia* 1991; **67**: 759–763.
14. Foth H, Geng WP, Krug N, Vetterlein F. Pulmonary uptake of bupivacaine in isolated perfused rat lung. *Naunyn Schmiedebergs Archives of Pharmacology* 1995; **351**: 99–106.
15. Geng WP, Ebke M, Foth H. Prolocaine elimination by isolated perfused rat lung and liver. *Naunyn Schmiedebergs Archives of Pharmacology* 1995: **351**: 93–98.
16. Kietzmann D, Foth H, Geng WP, Rathgeber J, Gundert-Remy U, Kettler D. Transpulmonary disposition of prilocaine, mepivcaine, and bupivacaine in humans in the course of extradural anaesthesia. *Acta Anaesthesiological Scandinavica* 1995; **39**: 885–890.
17. Schröder T, Hering JP, Hellige G. Hämodynamische Begleiterscheinungen intrakoronarer Injektionen eines neuen lungengängigen Ultraschallkonstrastmittels. *Ultraschall in der Medizin* 1995; **16**: 70–72.
18. Schröder T, Hering JP, Foth H, Ferrari M, Slipinková I, Hellige G. Peripheral and cardiac effects of a new phosphodiesterase inhibitor in comparison with enoximone. *Arzneimittel-Forschung* 1994; **44**: 948–950.

British Journal of Anaesthesia 1996; 77: 265–267

SHORT COMMUNICATIONS

Nitrous oxide produces a non-linear reduction in thiopentone requirements

T. KATOH AND K. IKEDA

Summary

We studied 88 healthy, ASA I patients (aged 20–45 yr), to determine if nitrous oxide affects thiopentone requirements for achieving 50% probability of no movement in response to verbal commands ($C_{P,50}$). Patients were allocated randomly to one of four nitrous oxide concentration groups (0%, 20%, 40% and 60%). Patients in each group were also allocated randomly to receive predetermined target plasma concentrations of thiopentone. Computer-controlled continuous infusion was used to maintain the target plasma thiopentone concentration, and this concentration was held constant for 6 min to ensure equilibration. The $C_{P,50}$ value of thiopentone in the absence of nitrous oxide was 14.8 μg ml^{-1}. The reduction in $C_{P,50}$ by nitrous oxide was non-linear, and the interaction coefficient between nitrous oxide and thiopentone was significantly smaller than zero ($P = 0.0274$), indicating that nitrous oxide antagonized the ability of thiopentone to prevent response to verbal commands. (*Br. J. Anaesth.* 1996; **77**: 265–267)

Key words

Anaesthetics gases, nitrous oxide. Anaesthetics i.v., thiopentone. Potency, anaesthetic.

General anaesthesia is often performed with a combination of inhalation and i.v. anaesthetics. When nitrous oxide is used in combination with thiopentone alone, intraoperative awareness is sometimes observed [1]. After a single dose of thiopentone, blood concentrations decrease exponentially. However, because of hysteresis between blood and brain concentrations, blood concentration is not a good predictor of brain concentration, and thus bolus administration of thiopentone does not permit its interactions with other drugs to be evaluated accurately. By using a pharmacokinetic model-driven computer-controlled infusion pump, it is possible rapidly to achieve and maintain a constant plasma concentration of thiopentone. Blood concentrations obtained while maintaining the plasma concentration stable can be used to undertake studies on the interactions between nitrous oxide and thiopentone. The aim of this study was to assess accurately the effects of nitrous oxide on the plasma concentration of thiopentone required to achieve a 50% probability of no movement in response to verbal commands ($C_{P,50}$).

Methods and results

After obtaining the approval of the local Ethics Committee and informed consent, we studied 88 patients of both sexes, ASA I, aged 20–45 yr, undergoing elective surgery. Patients did not receive premedication. An arterial cannula was inserted in the radial artery for blood sampling.

The 88 patients were allocated randomly to one of four groups. Patients in group 1 received no nitrous oxide, while those in groups 2, 3 and 4 received end-tidal concentrations of 20%, 40% and 60%, respectively. Patients in each group were also allocated randomly to receive predetermined target plasma concentrations of thiopentone. Thiopentone was infused using a computer-controlled infusion pump. Pharmacokinetic simulation and infusion algorithms made it possible rapidly to obtain and then maintain the target plasma concentration. The microcomputer was programmed with the thiopentone kinetic parameter set reported by Avram, Krejcie and Henthorn [2].

In group 1, patients breathed 100% oxygen throughout the study. In groups 2, 3 and 4, nitrous oxide was administered to achieve end-tidal concentrations of 20%, 40% and 60%, respectively. All patients breathed through a face mask connected to a semiclosed anaesthetic circuit. Concentrations of nitrous oxide, carbon dioxide and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac Ultima, Helsinki, Finland). In groups 2, 3 and 4, nitrous oxide was introduced after the patient had breathed 100% oxygen for 3 min. In group 1, thiopentone infusion was started 3 min after the start of oxygen, and in groups 2, 3 and 4, thiopentone infusion was started after the specified end-tidal nitrous oxide concentration had been maintained for more than 5 min. Infusion was regulated to maintain the target thiopentone concentration. At 5 min after the start of infusion, blood samples were obtained for measurement of thiopentone concentrations. At 10 min, patients were

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asked to open their eyes and blood samples were obtained. The patient's response to verbal command was recorded as positive or negative, with slight movement of the eyelids considered a negative response.

Plasma was separated immediately from blood and total plasma thiopentone concentrations were measured as soon as possible, usually within 4 h, using a high pressure liquid chromatographic assay with a sensitivity of 100 ng ml^{-1}. To ensure that stable plasma concentrations of thiopentone was maintained throughout infusion, the 5-min samples were compared with the 10-min samples. The mean concentration of the 5-min and 10-min samples was used for statistical analysis only if the concentration in the 5-min sample was within ±30% of that in the 10-min sample.

STATISTICAL ANALYSIS

The $C_{P,50}$ of thiopentone, and its reduction by nitrous oxide, were evaluated using the following multiple independent variable logistic regression model:

$$P(\text{no response}) = \frac{1}{1+e^{-Z}}$$

$$Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2$$

where $X_1 =$ measured plasma concentration of thiopentone, $X_2 =$ end-tidal nitrous oxide concentration, $\beta_0 =$ regression intercept constant, $\beta_1 =$ coefficient for thiopentone, $\beta_2 =$ coefficient for nitrous oxide and $\beta_{12} =$ coefficient for the product of the measured thiopentone and end-tidal nitrous oxide concentrations (interaction coefficient). The likelihood ratio test was applied to determine the independent variables to be removed from the model. $C_{P,50}$ for a given end-tidal nitrous oxide concentration was determined by setting the probability of no response to 0.5 and solving for thiopentone concentration as a function of the end-tidal nitrous oxide concentration as follows:

$$X_1 = \frac{-(\beta_0 + \beta_2 X_2)}{\beta_1 + \beta_{12} X_2}$$

Although a total of 88 patients were enrolled in the study, nine patients were excluded from the subsequent analysis because the measured thiopentone concentrations before and after verbal command were not within ±30%. In addition, one patient was eliminated from the study because of severe excitatory phenomena and vomiting. Thus the results of 78 patients are presented. This group included 48 men and 40 women with a mean age of 36 (range 20–45) yr and mean body weight of 56 (42–78) kg.

The logistic model was fitted to 78 data sets of observed response, measured plasma thiopentone concentration and end-tidal nitrous oxide concentration. The $C_{P,50}$ of thiopentone in the absence of nitrous oxide was 14.8 µg ml^{-1}. None of the three independent variables was removed from the model by the likelihood ratio test. The interaction coefficient β_{12} was significantly smaller than zero ($P =$ 0.0274). The reduction in the $C_{P,50}$ of thiopentone by nitrous oxide is presented in figure 1.

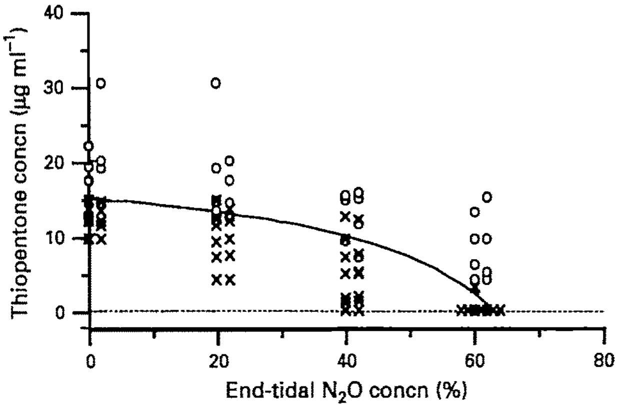

Figure 1 Plasma thiopentone concentration *vs* end-tidal nitrous oxide concentration for each patient. Each point represents the positive (movement (×)) or negative (no movement (0)) response for an individual patient. The line represents the maximum likelihood (logistic regression) solution for the reduction in $C_{P,50}$ of thiopentone by increasing concentrations of nitrous oxide.

Comment

The $C_{P,50}$ of thiopentone alone was found to be 14.8 µg ml^{-1}. The $C_{P,50}$ value determined in this study was almost identical to that obtained by Hung and colleagues using a similar technique [3]. The effect of nitrous oxide on the $C_{P,50}$ of thiopentone has not been documented previously. Nitrous oxide, however, has been shown to reduce the MAC_{awake} for isoflurane in a dose-dependent manner, with the MAC_{awake} reported as 67% [4]. Thus, 20%, 40% and 60% nitrous oxide should correspond to MAC_{awake} fractions of 0.3, 0.6 and 0.9, respectively. In a previous study, when nitrous oxide was administered together with isoflurane at an end-tidal concentration of 40%, the MAC_{awake} value for the combination of isoflurane and nitrous oxide was 18 (SEM 4)% greater than the value expected for simple additivity of the two agents [4]. This result indicates that the two anaesthetics are antagonistic with regard to this effect. We found that nitrous oxide reduced the $C_{P,50}$ in a dose-related manner. The interaction coefficient between thiopentone and nitrous oxide was significantly smaller than zero, indicating that nitrous oxide had a non-linear effect on reducing thiopentone requirements and that thiopentone requirements were greater than would be expected for simple additivity. Nitrous oxide appears to antagonize the ability of thiopentone to prevent responses to verbal commands. This may be caused by the ability of nitrous oxide to stimulate sympathetic activity. Hankala and co-workers found EEG evidence that nitrous oxide opposed the central nervous system depression produced by isoflurane [5]. Although there have been no reports that nitrous oxide reverses the central nervous system depression produced by thiopentone, this may offer a possible explanation for our findings.

In conclusion, nitrous oxide produced a non-linear reduction in thiopentone requirements for preventing response to verbal commands and the reduction was smaller than would be expected for simple additivity at low concentrations.

References

1. Warren TM, Datta S, Ostheimer GW, Naulty JS, Weiss JB, Morrison JA. Comparison of the maternal and neonatal effects of halothane, enflurane, and isoflurane for cesarean delivery. *Anesthesia and Analgesia* 1983; **62**: 516–520.
2. Avram MJ, Krejcie TC, Henthorn TK. The relationship of age to the pharmacokinetics of early drug distribution: The concurrent disposition of thiopental and indocyanine green. *Anesthesiology* 1991; **72**: 403–411.
3. Hung OR, Varvel JR, Shafer SL, Stanski DR. Thiopental pharmacodynamics. II. Quantitation of clinical and electroencephalographic depth of anesthesia. *Anesthesiology* 1992; **77**: 237–244.
4. Chortkoff BS, Bennett HL, Eger EI II. Does nitrous oxide antagonize isoflurane-induced suppression of learning? *Anesthesiology* 1993; **79**: 724–732.
5. Hankala AL, Lindgren L, Porkkala T, Jantti V. Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients. *British Journal of Anaesthesia* 1993; **70**: 54–57.

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Evaluation of two warming systems after cardiopulmonary bypass

E. L. Janke, S. N. Pilkington and D. C. Smith

Summary

We have compared the Thermomat electric undermattress (JMW Systems, Edinburgh, UK) and the Bair Hugger (Augustine Medical, Courtelary, Switzerland) forced-air warming blanket in 30 adult patients after cardiac surgery. All patients were warmed to an oesophageal temperature of 38 °C before termination of cardiopulmonary bypass (CPB); those with oesophageal temperatures < 35.5 °C at skin closure were allocated randomly to be rewarmed in the intensive care unit either on the Thermomat ($n = 15$) or under the Bair Hugger blanket ($n = 15$), at their highest settings. Oesophageal and lateral thigh skin temperatures were recorded every 15 min for 4 h. There was a significantly faster increase in core temperature (0.5 *vs* 0.75 °C h^{-1}; $P < 0.0002$) and skin temperature (0.86 *vs* 1.3 °C h^{-1}; $P < 0.001$) in the Bair Hugger group. However, there was no difference in the number of patients who reached a core temperature of 36 °C (15 Bair Hugger, 14 Thermomat) or 37 °C (11 Bair Hugger, seven Thermomat), or in the number of patients who reached a skin temperature of 37 °C in 4 h (four Bair Hugger, one Thermomat). Twelve patients in the Bair Hugger group reached a skin temperature of 36 °C compared with two in the Thermomat group ($P < 0.001$). The Bair Hugger warmed faster than the Thermomat both centrally and peripherally, and warmed more patients to a core temperature of 37 °C in 4 h, but did not reduce the time to tracheal extubation or alter important clinical aspects of postoperative course. (*Br. J. Anaesth.* 1996; **77**: 268–270)

Key words

Temperature, monitoring. Monitoring, temperature. Equipment, warming devices. Surgery, cardiovascular. Heart, cardiopulmonary bypass.

A decrease in temperature after cardiopulmonary bypass (CPB) is common; adequate rewarming may be difficult to achieve despite active intraoperative warming [1–3]. Residual hypothermia may delay drug clearance, impair coagulation and cause haemodynamic instability [4, 5]. We hypothesized that a forced-air convective system, such as the Bair Hugger, is a better means of warming adult patients after CPB in the intensive care unit (ICU) than a heated electric undermattress such as the Thermomat, which warms by conduction. This study was designed to determine if the Bair Hugger warming blanket is more effective than the Thermomat warming mattress in rendering adult patients normothermic who are hypothermic on arrival to the ICU after CPB.

Methods and results

After obtaining approval from the hospital Ethics Committee, we studied 30 adult patients with normal to moderately impaired left ventricular function undergoing hypothermic CPB for elective cardiac surgery. Premedication comprised a benzodiazepine and opioid; anaesthesia was induced with fentanyl 20–30 µg kg^{-1}, and midazolam 1–10 mg or thiopentone 25–100 mg, or both, and pancuronium was administered to provide neuromuscular block. Patients' lungs were ventilated with oxygen-enriched air (± isoflurane before bypass) with a heat–moisture exchanging filter; propofol 1–2 mg kg^{-1} was infused during CPB to maintain anaesthesia. Oesophageal (heart) and nasopharyngeal (brain) temperatures (Mon-a-therm General Purpose Critical Care Temperature Probes, Mallinckrodt Medical, Inc., Northampton, UK) were measured continually during operation. All patients were warmed actively to both oesophageal and nasopharyngeal temperatures of at least 38 °C before termination of bypass, using warm perfusion and a heated water mattress. Oesophageal temperature was used thereafter to measure core temperature, consistent with routine practice in our ICU. Patients with oesophageal temperatures < 35.5 °C at skin closure were allocated randomly to be rewarmed in the ICU either covered with a sheet and a cotton blanket, lying on the Thermomat mattress set at 41 °C (its highest setting) or using the Bair Hugger set on "high" (43 °C), placed directly on the patient and covered with a sheet and cotton blanket. Core and peripheral (skin, lateral aspect of thigh; Mon-a-therm, Mallinckrodt Medical, as above) temperatures were recorded every 15 min for 4 h or until normothermia (oesophageal temperature 37 °C) was achieved. The presence or absence of gross shivering, blood loss in the first 4 h and time to extubation were recorded. Sample size was determined by power analysis; 30 patients were required to detect a clinically relevant difference (one method warming patients to 36 °C core temperature 1 h faster than the other) with an 80% power of achieving a statistically significant result at the 5% level. The two sample *t* test was used to compare

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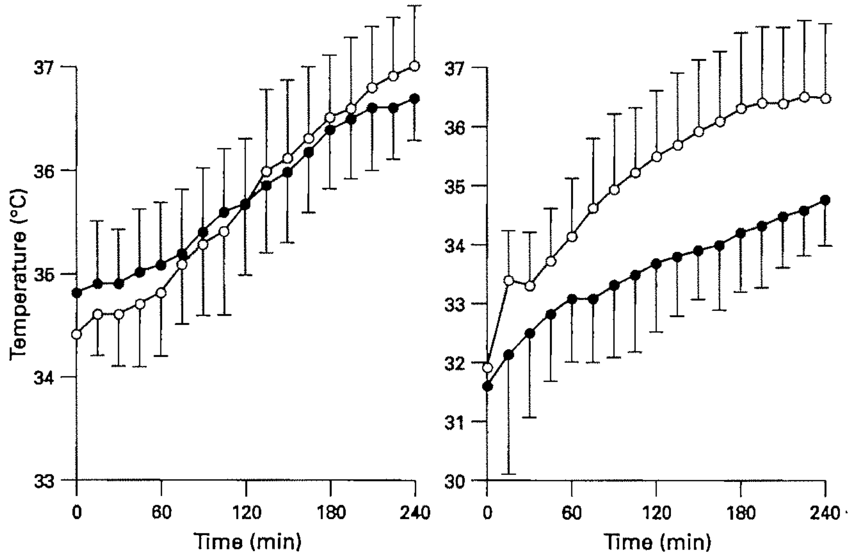

Figure 1 Comparison of changes in mean core temperature (left) and mean skin temperature (right) between the Bair Hugger group (○) and Thermomat (●) groups (mean, SD).

parametric data and rates of oesophageal and skin warming in each group. The chi-square test with Yates' correction was applied to compare non-parametric data. $P < 0.05$ was considered statistically significant.

There were no differences between the two groups in patient characteristics, treatment with inotropes or vasodilators, or incidence of postoperative shivering (two of 15; 13%). There was no difference in mean oesophageal temperature (34.8 °C for the Thermomat group, 34.4 °C for the Bair Hugger group; $P = 0.051$) or mean skin temperature (31.6 °C for the Thermomat group, 31.9 °C for the Bair Hugger group; $P = 0.5$) on arrival in the ITU, or a difference in core-to-skin temperature gap (3.2 °C for the Thermomat group, 2.5 °C for the Bair Hugger group; $P = 0.1$).

The number of patients reaching core temperatures of 36 °C (15 in the Bair Hugger group, 14 in the Thermomat group; $0.2 > P > 0.1$) and 37 °C (11 in the Bair Hugger group, seven in the Thermomat group; $0.1 > P > 0.05$), was not significantly different. Only two patients in the Thermomat group reached a skin temperature of 36 °C compared with 12 patients in the Bair Hugger group ($P < 0.001$). There was no difference in the number of patients who reached a peripheral temperature of 37 °C within 4 h (one patient in the Thermomat group, four patients in the Bair Hugger group; $0.2 > P > 0.1$). The mean rate of core temperature increase was 0.5 °C h^{-1} for patients in the Thermomat group and 0.75 °C h^{-1} in the Bair Hugger group ($P < 0.0002$). The mean rate of increase in skin temperature was 0.86 °C h^{-1} for the Thermomat group and 1.3 °C h^{-1} for the Bair Hugger group ($P < 0.001$). A comparison of mean temperatures for each group over time is shown in figure 1.

Comment

Patients undergoing CPB are unique in that intentional systemic hypothermia occurs with an open chest cavity; for part of this time the lungs are not ventilated and the heart is actively cooled separately. Even with aggressive central and peripheral warming, there is ongoing heat loss after bypass, during wound closure and transport to the ITU. Subsequent temperature equilibration between the core and periphery may result in a decrease in core temperature, sometimes rapidly. Behavioural and physiological responses to hypothermia are often undesirable in cardiac patients and may be ablated in the ITU by residual anaesthetic agents, vasodilators, sedation and neuromuscular block. Shivering may be intentionally abolished because it increases the body's oxygen demand by 400–500% [6]; it may also promote respiratory acidosis from increased carbon dioxide production. Ordinarily, spontaneous arrhythmias are not seen until core temperature has decreased to approximately 33 °C. In patients who have had open heart surgery, ischaemia, acid–base or electrolyte abnormalities, or other co-existing factors, may contribute to myocardial irritability. Other physiological changes associated with hypothermia such as altered blood-gas transport, increased blood viscosity and mental status changes, do not occur until reductions in body temperature are extreme [4].

Conductive heat transfer occurs by direct contact between objects; in the intraoperative period, heat is lost in this way to the operating table and underlying wet sheets, cool i.v. fluids and irrigating solutions. The heat supply of a warming mattress (a conducting surface) is limited by skin conductance, temperature gradient and contact area. To prevent burns, a sheet is usually interposed between the mattress and the patient, interfering with heat transfer. Additionally, peripheral vasoconstriction may further reduce the effectiveness of a warming mattress as a heat exchanger. A warming mattress can be warmed on the bed before the patient is transferred to it, but removal of the warming mattress from under the patient can be cumbersome. However, the mattress may stay in place during most routine postoperative care in the ICU. Convective heat exchange involves the direct transfer of energy by collisions between body surface molecules and moving air molecules. Air velocity, ambient temperature and surface area are its main determinants. The forced-air warming mattresses currently available are lightweight and easy to use, although they are often partially removed or displaced in the ICU for certain aspects of care, potentially decreasing their effectiveness as a means of warming.

Although our study showed a faster rate of both core and peripheral warming by the Bair Hugger, there was no difference in the time to tracheal extubation or in the overall nature of the postoperative course between the two groups. This suggests that both a heated electric undermattress and a forced-air warming blanket are appropriate methods of warming hypothermic patients after bypass in the ICU.

References

1. Joachimsson PO, Nystrom SO, Tyden H. Postoperative ventilatory and circulatory effects of extended rewarming during CPB. *Canadian Journal of Anaesthesia* 1989; **36**: 9–19.
2. Ralley FE, Ramsay JG, Wynands JE, Townsend E, Whalley DG, DelliColli R. Effect of heated, humidified gases on temperature drop after cardiopulmonary bypass. *Anesthesia and Analgesia* 1984; **63**: 1106–1110.
3. Noback CR, Tinker JH. Hypothermia after cardiopulmonary bypass in man: amelioration by nitroprusside-induced vasodilation during rewarming. *Anesthesiology* 1980; **53**: 277–280.
4. Morley-Forster PK. Unintentional hypothermia in the operating room. *Canadian Anaesthetists Society Journal* 1986; **33**: 516–527.
5. Valeri CR, Khabbaz, Khuri SF, Marquardt C, Ragno G, Feingold H, Gray AD, Axford T. Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. *Journal of Thoracic and Cardiovascular Surgery* 1992; **104**: 516–527.
6. Bay JB, Nunn JF, Prys-Roberts C. Factors influencing arterial PO_2 during recovery from anaesthesia. *British Journal of Anaesthesia* 1968; **40**: 398–406.

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Calcium homeostasis during i.v. infusion of 1.5% glycine in anaesthetized pigs

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Summary

We have examined changes in plasma concentrations of calcium in seven anaesthetized pigs during i.v. infusion of irrigating fluid containing 1.5% glycine. Volumes infused were 875 ml at 20 min (22 ml kg^{-1}), 1475 ml at 40 min and 2075 ml at 60 min (75 ml kg^{-1}). Plasma concentrations of sodium decreased from 134.5 (SD 3.4) to 112.8 (6.7) mmol $litre^{-1}$ at 60 min and correlated with the volume of glycine infused ($r^2 = 0.73$; $P < 0.0001$). Changes in total calcium concentrations were not statistically significant. A decrease in ionized calcium concentration was observed at 40 min (1.12 (0.05) *vs* 1.24 (0.04) mmol $litre^{-1}$; $P < 0.05$) and reached 1.11 (0.05) mmol $litre^{-1}$ at 60 min ($P < 0.01$). However, when corrected for pH, this decrease was not statistically significant. These results suggest that changes in plasma concentrations of sodium rather than changes in calcium homeostasis are probably more important in the development of transurethral prostatic syndrome. (*Br. J. Anaesth.* 1996; **77**: 271–273)

Key words

Complications, hypocalcaemia. Complications, hyponatraemia. Ions, calcium. Surgery, urological. Pig.

Resection of the prostate or endometrium by resectoscope is a technique which requires the use of electrically inert near-isotonic solutions for irrigation. Resorption into the patient's body of a large amount of glycine-containing irrigating fluid used for these procedures has been reported [1]. This complication includes biological disturbances such as dilutional hyponatraemia and hypo-osmolality [1]. Some clinical observations suggested that hypocalcaemia could be associated with these plasma disturbances [2]. However, there has been no controlled study evaluating calcium changes during i.v. infusion of irrigating fluid. In this study, we assessed the acute effects of i.v. infusion of glycine on calcium homeostasis in anaesthetized pigs.

Methods and results

After obtaining approval from our institution's Animal Care Committee, we studied seven pigs (23–25 kg). Ketamine 8 mg kg^{-1} was given i.m. after a 12-h fast. Anaesthesia was induced with propofol 5 mg kg^{-1} i.v., sufentanil 3 µg kg^{-1} i.v. and pancuronium 0.1 mg kg^{-1} i.v., and was maintained with propofol 10 mg^{-1} kg^{-1} h^{-1}. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4–5%.

A femoral vein and artery were cannulated to provide arterial pressure monitoring, arterial blood samples and a route for administration of glycine. Arterial blood samples were obtained for baseline measurements before a dose of 500 ml of 1.5% glycine (Glycocolle 1.5%, Baxter, Maurepas, France) was infused over 5 min, followed by a constant infusion of 1500 ml h^{-1} over 55 min. This corresponds to an infusion rate of 34 ml kg^{-1} during the first 20 min and 75 ml kg^{-1} over the whole study. Repeated measurements were made 20, 40 and 60 min after the beginning of the infusion of glycine. Samples of blood for measurement of ionized calcium and pH-normalized ionized calcium concentrations were obtained anaerobically into preheparinized syringes and analysed immediately using the ICA II instrument (Copenhagen, Denmark). Plasma concentrations of sodium, potassium, magnesium, calcium, chloride, urea, protein, bicarbonate and blood glucose were analysed using the Astra 8 chemistry instrument (Beckman, Schiller Park, IL, USA). Pa_{O_2}, Pa_{CO_2} and arterial pH were measured using a Radiometer ABL electrode system (Copenhagen, Denmark). The concentration of ammonia in blood was measured by the ACA III instrument (Du Pont, Wilmington, DE, USA). Osmolality was calculated using a standard formula: osmolality (mosmol $litre^{-1}$) = (sodium mmol $litre^{-1}$ × 2) + urea mmol $litre^{-1}$ + blood glucose mmol $litre^{-1}$.

Statistical significance was determined using analysis of variance (ANOVA) for repeated measures followed by Dunn's test. $P < 0.05$ was considered statistically significant. Relationships between electrolyte concentrations and volume of glycine infused were assessed using Pearson's product correlation coefficient (r) and coefficient of determination (r^2).

During the first 20 min of i.v. infusion (875 ml), there was a significant decrease in mean plasma concentrations of sodium from 134.5 (SD 3.4) to 121.2 (4.0) mmol $litre^{-1}$ ($P < 0.05$). At 40 min (1375 ml perfused), pigs demonstrated a more

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Table 1 Changes in serum concentrations of protein, osmolality, calcium and other electrolytes during i.v. infusion of 1.5% glycine (mean (SD) and *median* (range)). The volumes infused were 875 ml at 20 min, 1475 ml at 40 min and 2075 ml of 60 min. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with baseline.

	Sodium (mmol litre^{-1})	Protein (g litre^{-1})	Osmolality (mosmol litre^{-1})	Magnesium (mmol litre^{-1})	Potassium (mmol litre^{-1})	Calcium (mmol litre^{-1})	Ionized calcium (mmol litre^{-1})	pH-normalized ionized calcium (mmol litre^{-1})
Normal range	135–145	60–76	290–310	0.75–1.00	3.5–4.5	2.15–2.55	1.00–1.30	1.00–1.30
Baseline	134.5 (3.4)	55.3 (5.1)	278.7 (8.4)	0.7 (0.1)	4.4 (0.8)	2.30 (0.27)	1.24 (0.04)	1.28 (0.07)
	134 (130–140)	*54.8* (49.3–63.7)	*277.4* (268–288)	*0.70* (0.58–0.89)	*4.4* (3.7–6.1)	*2.35* (1.74–2.60)	*1.25* (1.19–1.31)	*1.28* (1.19–1.42)
20 min	121.3 (4.0)*	46.0 (4.6)	251.3 (7.7)	0.56 (0.09)	4.3 (0.2)	2.10 (0.14)	1.13 (0.04)	1.16 (0.07)
	122 (116–127)	*45.1* (41–52.5)	*246* (237–262)	*0.58* (0.39–0.68)	*4.2* (4.1–4.7)	*2.07* (1.84–2.25)	*1.14* (1.07–1.20)	*1.13* (1.06–1.26)
40 min	117.7 (4.8)*	44.5 (5.1)	244.1 (9.0)*	0.57 (0.06)	4.5 (0.4)	2.09 (0.17)	1.12 (0.05)*	1.16 (0.07)
	119 (111–124)	*44.2* (38–53.5)	*241* (228–254)	*0.59* (0.48–0.66)	*4.5* (4.1–5.4)	*2.11* (1.81–2.27)	*1.13* (1.05–1.20)	*1.16* (1.07–1.27)
60 min	112.8 (6.7)**	43.8 (5.3)	234.2 (11.6)***	0.58 (0.07)	4.6 (0.4)	2.00 (0.22)	1.11 (0.05)**	1.15 (0.08)
	113 (106–121)	*42.8* (38–52.3)	*226.5* (219–248)	*0.58* (0.49–0.71)	*4.6* (4.1–5.2)	*1.97* (1.72–2.27)	*1.11* (1.03–1.20)	*1.16* (1.05–1.27)

marked decrease in plasma concentrations of sodium of 17 mmol ($P < 0.05$). At 60 min (1875 ml perfused), this decrease was 22 mmol (mean plasma sodium concentration 112.8 (6.7) mmol litre^{-1}) ($P < 0.001$). This decrease was correlated significantly with the volume of glycine infused ($r = 0.85$, $r^2 = 0.73$, $P < 0.0001$). A statistically significant decrease in calculated osmolality was seen at 40 min ($P < 0.05$) and 60 min ($P < 0.001$). Protein, urea, ammonia and other electrolyte concentrations, including potassium, magnesium and phosphate, did not change significantly from baseline during the study (table 1).

A 12% decrease in plasma concentrations of calcium occurred after infusion of glycine but this decrease was not significant (table 1). In contrast, ionized calcium decreased significantly at 40 min but remained greater than 1.10 mmol litre^{-1}. When ionized calcium was correlated for arterial pH, there was no significant change.

There were no statistically significant correlations between calcium, ionized calcium or pH-corrected ionized calcium, and volume of glycine infused ($r = -0.46$, -0.68, -0.54 and $r^2 = 0.21$, 0.46, 0.29, respectively) and no relationship between ionized calcium and changes in serum protein concentration.

Comment

It is generally believed that transurethral resection of the prostate syndrome (TURPS) is the results of dilutional hyponatraemia caused by the direct toxicity of glycine and by hyperammonia [1]. Recently, hypocalcaemia has been proposed in the physiopathology of TURPS [2].

Hypocalcaemia denotes low concentrations of biologically active calcium in blood. In fact, symptoms caused by altered concentrations of calcium reflect changes in the serum concentration of ionized calcium [3]. Only one case report expressed interest in the ionized calcium concentration rather than the total calcium concentration during TURPS [2].

In this study, we evaluated changes in plasma calcium concentrations during i.v. infusion of 1.5% glycine. We found no statistically significant changes in serum calcium concentrations throughout the study. However, a significant decrease in ionized calcium was noted after infusion of glycine 1475 ml over 40 min. Nevertheless, concentrations of ionized calcium were in the normal range for our laboratory and pH-normalized ionized calcium was not decreased significantly by infusion of glycine. Thus, within the limitations of our study, we found that infusion of glycine was not associated with significant disturbances in serum calcium.

Few studies have examinated calcium homeostasis during absorption of irrigating solutions such as glycine, despite the crucial role of calcium in neurological and cardiovascular function. Malone and colleagues reported a peroperative decrease in plasma calcium; further changes were not observed in the postoperative period [4]. In seven healthy volunteers, glycine 1 litre i.v. over 20 min (20 ml kg^{-1}) significantly decreased plasma concentrations of calcium [5]. A decrease in plasma calcium concentration (2.04 *vs* 2.16 mmol litre^{-1}) was also seen after 1.57 litre (22 ml kg^{-1}) of fluid absorption [6]. The clinical significance of these studies is limited as none measured pH-normalized ionized calcium.

Several events may induce acute hypocalcaemia during anaesthesia: transient hypomagnesaemia, an increase in plasma albumin concentration, administration of citrate and hyperphosphataemia are more common causes [3]. It must be remembered that the concentration of ionized calcium is dependent on arterial pH: acidosis increases and alkalosis decreases the concentration. In our study, none of these factors was present: phosphorus concentration was decreased and the decrease in plasma magnesium concentration was not statistically significant.

Volumes of glycine absorbed during TURPS are generally 500–4000 ml [1, 6]. The volumes administered in our animal study were 875 ml at 20 min and 1875 ml at 60 min (34 and 75 ml kg^{-1}). For humans weighing 60–70 kg, this corresponds to values of 2000–5000 ml. Moreover, serum concentrations of sodium were less than 120 mmol litre^{-1}, a value known to be the threshold for the development of TURPS [1]. Despite this, calcium homeostasis was not altered.

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References

1. Hahn RG. The transurethral resection syndrome. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 567–567.
2. Krohn JS. Dilutional hypocalcemia in association with dilutional hyponatremia. *Anesthesiology* 1993; **79**: 1136–1138.
3. Guyton AC. *Textbook of Medical Physiology*. Philadelphia: WB Saunders, 1991; 878–879.
4. Malone PR, Davies JH, Standfield NJ, Bush RA, Gosling JV, Shearer RJ. Metabolic consequences of forced diuresis following prostatectomy. *British Journal of Urology* 1986; **58**: 406–411.
5. Hahn RG, Stalberg HP, Gustafsson SA. Intravenous infusion of irrigating fluids containing glycine or mannitol with and without ethanol. *Journal of Urology* 1989; **142**: 1102–1105.
6. Ghanem AN, Ward JP. Osmotric and metabolic sequelae of volumetric overload in relation to the TURP syndrome. *British Journal of Urology* 1990; **66**: 71–78.

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CASE REPORTS

Cardiac arrest after Caesarean section under subarachnoid block

T. J. SCULL AND F. CARLI

Summary

Cardiac arrest occurred on arrival in the recovery room after emergency Caesarean section under subarachnoid block. The patient was resuscitated successfully and recovered with no adverse effects. The current literature is reviewed and the pathophysiological mechanisms involved in the aetiology of cardiac arrest under subarachnoid block are discussed. Early use of adrenaline to treat severe bradycardia or hypotension is recommended. (*Br. J. Anaesth.* 1996; **77**: 274–276)

Key words

Anaesthesia, obstetric. Complications, cardiac arrest. Anaesthetic techniques, subarachnoid.

Subarachnoid anaesthesia is a widely practised technique for both elective and emergency procedures. It is recommended for both its efficacy and safety [1, 2]. Haemodynamic instability and cardiac arrest have been reported in healthy patients [3]. Occasional case reports [3–5] and a series of patients experiencing cardiac arrest [6] have been reported in the American literature, but there is little in the European journals. We report a case of cardiac arrest, occurring in a parturient after a Caesarean section under subarachnoid block.

Case report

A 31-yr-old Afro-Caribbean woman (weight 76 kg, height 1.68 m), ASA I, presented at term in spontaneous labour. This was her second pregnancy; her first had resulted in a vaginal delivery and the course of the second had been uneventful.

On arrival in the delivery suite she was in active labour, her cervix was dilated 6 cm and her membranes were bulging. These were ruptured and fetal monitoring, via a scalp electrode, commenced. Over the next 8 h, progress was slow, dilatation increasing to 8 cm. The baby showed signs of distress which were manifested as type 2 decelerations, and it was decided to deliver the baby by Caesarean section.

Subarachnoid anaesthesia was commenced using a 27-gauge Quinke needle with 0.75% hyperbaric bupivacaine 2 ml and preservative-free morphine 0.25 mg. Bilateral sensory block to temperature from T2 to S5 was obtained. After positioning the patient in the supine position, with left lateral wedging, Caesarean section was carried out, and a boy (3585 g) with Apgar scores of 9 at both 1 and 5 min was delivered. Arterial pressure, ECG and oxygen saturation were monitored throughout the procedure. Systolic arterial pressure was 110–120 mm Hg and heart rate 70–110 beat min^{-1}. Saline 0.9% (2 litre) and three boluses of ephedrine 5 mg were required to maintain stability. After delivery, an infusion of Syntocinon 20 u. in normal saline 1 litre was started. The duration of Caesarean section was 1 h 35 min and estimated blood loss was 700 ml. The patient's vital signs before leaving the operating theatre were: arterial pressure 110/60 mm Hg, heart rate 105 beat min^{-1} and Sp_{O_2} 96%. The patient was then transferred to the adjacent recovery room in a semi-reclined position, fully conscious, conversing and holding her baby. As monitoring was being re-established, she suddenly became unresponsive, with no palpable pulse and no respiratory effort.

Cardiopulmonary resuscitation was initiated and her trachea was intubated within 2 min. ECG revealed the initial rhythm to be ventricular fibrillation and she received four dc shocks, adrenaline 2 mg i.v., naloxone 0.4 mg i.v. and lignocaine 100 mg i.v. At 9 min after cardiac arrest her rhythm had converted to sinus tachycardia, with a strong pulse. She was then transferred to the intensive care unit.

A series of investigations was carried out to identify the cause; ECG revealed a sinus tachycardia with no acute changes, echocardiogram showed good left ventricular function (ejection fraction 55–60%), with normal valvular morphology and function. Serum electrolyte concentrations were within normal limits, except for a low serum magnesium concentration of 0.25 mmol litre^{-1} (normal 0.75–1.25 mmol litre^{-1}) obtained at the time of cardiac arrest. A CT scan revealed minimal cerebral oedema, and a ventilation–perfusion scan of the lungs was normal.

The patient's lungs were ventilated for 20 h and she remained haemodynamically stable without need of inotropic support. After tracheal extubation she was confused, with no memory of the preceding events. Her cognitive function returned to normal over the following week. Despite extensive investi-

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gation, no obvious cause of the arrest was found, other than the low magnesium concentration, the aetiology of which was unclear. In the postoperative period she developed a wound infection that necessitated a prolonged hospital stay. She was discharged home 25 days after her section and remains well.

Discussion

Cardiac arrest during subarachnoid anaesthesia is an uncommon but well reported phenomenon. Bradycardia with resultant hypotension is thought to occur by two mechanisms. The first involves block of the cardioacceleratory sympathetic fibres, which may occur with a sensory block as low as T10, as it has been shown that the sensory–sympathetic differential may be up to six segments [7]. This allows unopposed parasympathetic input with a negative chronotropic effect. The other mechanism is a manifestation of decreased venous return, which may trigger reflexes mediated by caval and atrial receptors [8], and the pacemaker stretch reflex [9]. Acute reductions in venous return have also been reported to activate the Benzold–Jarish reflex with resultant bradycardia [10].

Excessive bradycardia progressing to asystole has been well documented recently [3, 4]. In some reports [3–5], patients responded promptly to atropine, ephedrine and external cardiac massage, cardiac output and consciousness being rapidly restored with no sequelae after the event. The series of patients reported by Caplan and colleagues [6], as a result of closed claims analysis, exhibited a different outcome and possibly a different pathogenesis. These patients showed marked similarities; all were young (mean age 35 yr), healthy (ASA I or II), had high sensory block, and all experienced a poor outcome; six died and seven were severely neurologically damaged. Close scrutiny of these cases implicated the use of sedation with opioids or benzodiazepines, with a resulting respiratory insufficiency, to be possible causative factors in 50 % of the cases [6, 12]. In addition, another 22 cases from closed claims analysis have recently been reported [11]. These patients had similar characteristics and outcomes to the initial series of 13. Pulse oximetry failed to demonstrate desaturation and it was concluded that "one or more circulatory mechanisms played an important role in these events."

Our patient had some factors in common with the "Caplan groups". The patient was young, haemodynamically stable, with a high sensory block, but outcome was good. Cases of cardiac arrest after subarachnoid block that required protracted resuscitation and had a good outcome are rare. Perhaps this represents a lack of reporting or indicates that a high sympathetic block in some way complicates successful resuscitation.

Detailed analysis of the closed claim cases reveals the importance of warning signs of the forthcoming arrest, usually bradycardia or hypotension in the preceding 1–2 min. Our case was in transfer to recovery during this phase, with no monitoring in place and it is therefore not possible to comment on the presence or absence of these signs.

We believe that the patient suffered a primary cardiac arrest. In the period immediately after the arrest she received treatment with i.v. naloxone, but we do not feel that respiratory depression secondary to intrathecal opioids played any aetiological role in the chain of events. It may be significant that our patient experienced the cardiac arrest shortly after repositioning had occurred. In this unit it is customary to roll the patient from side to side in order to clean the abdomen, and then to transfer the patient to the recovery area in a semi-reclined position, approximately 30° head-up. These positional changes may have resulted in alterations in venous return and triggering of the above-mentioned reflexes, causing bradycardia and hypotension. Blood loss in the presence of sympathetic block may lead to hypotension, however only 700 ml was lost over a 1–1.5-h period, and adequate replacement was achieved.

Hypomagnesaemia at the time of the arrest was the only electrolytic abnormality. This is associated with cardiac arrhythmias, and is known to prolong QT intervals [12]. In addition to cardiac signs, patients usually complain of weakness and tremors and exhibit muscle fasciculation. The patient had none of these signs or symptoms, which makes it difficult to conclude that this was the cause.

The series of patients reported by Caplan and colleagues [6] did not receive adrenaline until approximately 8 min had passed after recognition of the cardiac arrest; a perfusing rhythm was re-established within approximately 3 min of this treatment. We feel that the early use of adrenaline and the prompt resuscitative efforts were important factors in the positive outcome of our patient.

We would like to support the approach advocated by Caplan and colleagues that the potent α and β agonist adrenaline be used early in the treatment of extreme bradycardia and hypotension in patients with high sympathetic block, especially if initial treatment with ephedrine or atropine has been ineffective.

References

1. Moore DC. Spinal (subarachnoid) block; a review of 11,574 cases. *Journal of the American Medical Association* 1966; **195**: 907.
2. Wilkinson WN. Two thousand spinal anaesthetics. *British Journal of Anaesthesia* 1963; **35**: 711.
3. Mackey DC, Carpenter RL, Thompson GE, Brown DL, Bodily MN. Bradycardia and asystole during spinal anesthesia: a report of three cases without morbidity. *Anesthesiology* 1989; **70**: 866–868.
4. Nishikawa T, Anzai Y, Namiki A. Asystole during spinal anaesthesia after change from Trendelenburg to horizontal position. *Canadian Journal of Anaesthesia* 1988; **35**: 406–408.
5. Gibbons JJ, Ditto FF. Sudden asystole after spinal anesthesia treated with the "pacing thump". *Anesthesiology* 1991; **75**: 705.
6. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. *Anesthesiology* 1988; **68**: 5–11.
7. Chamberlain DP, Chamberlain BDL. Changes in the skin temperature of the trunk, and their relationship to sympathetic blockade during spinal anesthesia. *Anesthesiology* 1986; **65**: 139–143.
8. Kappagoda CT, Linden RJ, Snow HM. A reflex increase in

heart rate from distention of the junction between the superior vena cava and the right atrium. *Journal of Physiology* (*London*) 1972; **220**: 177–197.

9. Pathak DL. Autoregulation of chronotropic response of the heart through pacemaker stretch. *Cardiology* 1973; **48**: 45–64.
10. Mark AL. The Benzold–Jarish reflex revisited: Clinical implications of inhibitory reflexes originating in the heart. *Journal of the American College of Cardiology* 1983; **1**: 90–102.
11. Caplan RA. Adverse outcomes in anesthesia practice. Annual refresher course of lectures. Atlanta, GA: American Society of Anesthesiologists, 1995; 254.
12. Knill RL. Cardiac arrests during spinal anesthesia; unexpected? *Anaesthesiology* 1988; **69**: 629.
13. Seelig MS. Electrocardiographic patterns of magnesium depletion appearing in alcoholic heart disease. *Annals of the New York Academy of Science* 1969; **162**: 906.

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Severe systemic cholesterol embolization after open heart surgery

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Summary

Cholesterol crystal embolization (CCE) may be triggered by various factors: intra-arterial angiographic procedures, aortic or vascular surgery, anticoagulant or thrombolytic treatments, or both. There are few previous reports of patients undergoing coronary artery bypass grafting (CABG) experiencing and therefore displaying severe systemic CCE. We describe four patients presenting, shortly after CABG, cutaneous, renal, neurological and hepatic signs related to severe CCE confirmed by skin biopsy. All patients died 11–92 days after surgery. As systemic CCE reveals severe atheromatous disease and is associated with a poor prognosis, it is advisable to avoid CABG in patients who present symptoms of CCE before surgery. (*Br. J. Anaesth.* 1996; **77**: 277–280)

Key words

Heart, coronary artery bypass. Surgery, cardiovascular. Complications, cholesterol crystal embolization.

An eroded atheromatous aorta may be a source of cholesterol crystal embolism (CCE). Embolization of atheromatous material accounts for obstruction of distal arterioles around which a foreign-body giant cell granuloma inflammatory reaction develops. The diagnosis is often delayed or unrecognized because of varying or misleading clinical signs, such as renal insufficiency, digestive or neurological symptoms, or both, or unexplained multiple-system disease [1]. Various triggering factors have been described such as intra-arterial angiographic procedures, aortic or vascular surgery, and in some cases anticoagulant or thrombolytic treatments, or both.

Patients undergoing coronary artery bypass grafting (CABG) often experience a combination of these factors: anticoagulation—before, during and after surgery—intra-arterial angiographic procedures and intraoperative aortic cross-clamping. These multiple factors could account for the acute and severe postoperative clinical and biological findings observed in the four patients described here.

Case report

From September 1992 to January 1994, four patients developed very severe and acute systemic cholesterol embolization immediately after CABG. All were male with a mean age of 67 yr (range 62–71 yr). They presented at least two risk factors for atherosclerosis, and a previous history of atheromatous disease (coronary artery disease $n = 4$, chronic peripheral arterial disease $n = 2$, carotid vascular surgery $n = 1$) (table 1). These four patients were referred to our institution for unstable angina and therefore received i.v. heparin.

A coronary angiogram was performed in all cases, 3–5 days after admission. During catheterization, patient No. 1 complained of chills and myalgias, and patient No. 3 experienced a transient cerebrovascular ischaemic accident. Multiple coronary artery disease was noted in all patients; patient No. 2 also presented severe stenosis of the left main coronary artery. Patient Nos 3 and 4 experienced a blue toe syndrome with normal peripheral pulses and renal insufficiency (serum creatinine concentration 344 μmol litre^{-1} and 281 μmol litre^{-1}, respectively) shortly after left heart catheterization, before surgery.

All patients underwent CABG 2–55 days after coronary angiogram. The immediate postoperative course was complicated in all cases: patient No. 2 presented an unstable haemodynamic status related to intraoperative myocardial infarction (confirmed by postmortem examination) which required intra-aortic balloon counterpulsation. All patients had postoperative coma, acute renal insufficiency and required haemodialysis, a highly elevated serum creatine kinase activity (patient Nos 2 and 4) and purple toes accompanied by more diffuse cyanotic mottling of the surrounding skin (livedo reticularis); peripheral pulses were normal. In addition, severe abnormalities of hepatic (elevated serum bilirubin concentration) and pancreatic (elevated serum amylase activities of 367 iu litre^{-1}) functions were observed in patient No. 1. Elevated erythrocyte sedimentation rate (ESR), transient peripheral blood eosinophilia (450 eosinophils mm^{-3}) and low C_3 complement fraction were present in patient Nos 1 and 2 (table 2, fig. 1). Systemic cholesterol embolization was confirmed in all patients by skin biopsy which showed acute inflammation with cholesterol clefts within small arterioles.

Patient management included interruption of heparin, and administration of antiplatelet agents (aspirin) and methylprednisolone 80–120 mg day^{-1}.

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Table 1 Patient characteristics. AMI = Acute myocardial infarction; 1 = risk factor present

Patient No.	Age (yr)	Risk factors of atherosclerosis				Previous history
		Hypertension	Diabetes	Smoking	Hyperlipidaemia	
1	67	1	1	1	1	Angina
2	69	1	1	1	—	Angina, AMI
3	71	1	—	1	1	Angina, chronic peripheral arterial disease
4	62	1	—	1	—	Carotid endarterectomy, femoropopliteal bypass grafting

Table 2 Laboratory findings. Values are peak levels obtained. ASAT = serum aspartate aminotransferase activity; ALAT = serum alanine aminotransferase activity; CK = serum creatinine kinase activity; ESR = erythrocyte sedimentation rate

Patient No.	Creatinine (μmol litre^{-1})	ASAT (iu litre^{-1})	ALAT (iu litre^{-1})	Total CK (iu litre^{-1})	ESR (mm)	Eosinophils (/mm^3)
1	495	14240	3580	859	64	1105
2	631	218	56	7162	105	541
3	525	43	57	258	44	460
4	656	320	37	1956	25	380

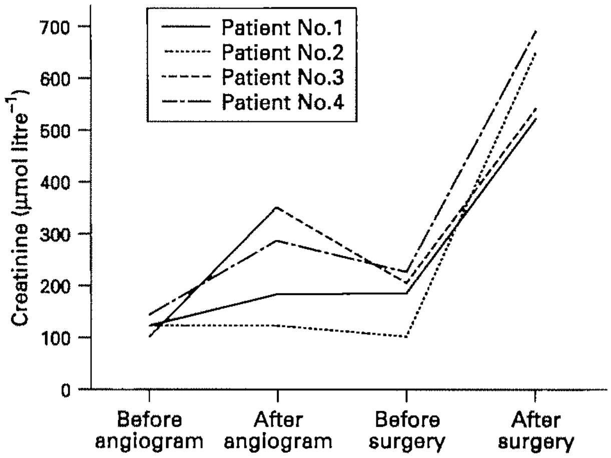

Figure 1 Serum concentrations of creatinine before and after coronary angiogram and surgery.

With this treatment, clinical and biological improvements occurred in patient Nos 1 and 3: weaning from haemodialysis and neurological improvement (normal consciousness although both had persistent hemiplegia). However, this treatment failed in patient Nos 2 and 4. All patients died within 11–92 days after surgery: patient No. 1 died from mesenteric infarction, patient Nos 2 and 4 from sudden death, and patient No. 3 from a cerebrovascular accident.

Discussion

Embolic migration of cholesterol crystals has been commonly accepted after experimental work carried out by Flory [2] and Snyder and Shapiro [3], in addition to pathological studies [4]. Cholesterol crystals obstruct 100–250 µm size arterioles. As their elimination occurs very slowly, a local foreign-body type inflammation develops, completing arteriolar obstruction. Cholesterol crystals may be released into the vascular lumen in response to rupture of the atherosclerotic plaque related to intraplaque haemorrhage or confined dissection.

CCE occurs in patients with diffuse atherosclerosis and multiple vascular risk factors (high cholesterol concentration, diabetes, tobacco abuse, hypertension) exposed to a triggering agent [5]. This diffuse embolization of atheromatous material may therefore be responsible for various clinical manifestations including: "blue toes syndrome" together with normal peripheral pulses associated with livedo reticularis of the lower limbs; renal insufficiency with severe arterial hypertension; digestive or neurological symptoms, or both; or even "fever of an unknown origin", therefore mimicking diffuse vasculitis [1] or infective endocarditis. Diagnosis may be very difficult [6] and this complications has to be borne in mind by practitioners. The onset of such clinical features is usually insidious, although acute and severe clinical manifestations after cardiac angiography have been reported [7]. Pathological [4] and clinical observations [8] support the existence of such triggering factors. Thus angiographic procedures (aortography, left heart catheterization), aortic and vascular surgery have commonly been related to the occurrence of CCE [9].

In the literature, angiographic procedures accounted for 50% of cases of CCE [10, 11]; the mean delay between the invasive procedure and symptoms was 13.5±21 days (range 1 h to 3 months). Guidewire and catheter manipulations injure the endothelium and therefore dislodge soft cholesterol material.

Aortic surgery was responsible for 9% of CCE cases published until 1988 [10, 11], but this has since reached 18% among published cases. Aortic surgery was always preceded by an angiographic procedure; aortic cross-clamping and also incision of the artery releases the atheromatous material into the bloodstream [12].

Anticoagulant therapy as a triggering factor of

CCE was first suggested in 1961 by Feder and Auerbach [13]. They reported six cases of "purple toes" with normal peripheral pulses occurring 3–8 weeks after introduction of anticoagulant treatment. Anticoagulant treatment (heparin or antivitamin K, or both) was given in 19% of published case reports [10, 11]. These medications are often associated with another triggering factor, in most cases an angiographic procedure [5, 7, 9, 14]. There are several case reports in the literature [1, 5, 13–16] in which anticoagulant therapy was the sole triggering factor. However, postmortem studies [4] failed to show any difference in the atheroembolic rate according to whether or not anticoagulants were given. This complication seems rare in view of the large number of patients treated.

Thrombolytic therapy was suspected to be an atheroembolism triggering factor as early as 1976 by Spangen and colleagues [17], who observed worsening renal function after i.v. streptokinase therapy. The first well documented case was described in 1979 and involved a patient treated with streptokinase for severe pulmonary embolism [18]. Since then, some cases indicating thrombolytic therapy as the triggering factor for CCE have been reported. In several cases, this therapy was associated with an angiographic procedure [19]; thrombolytic therapy was the sole triggering factor in other cases [20–24]. The underlying pathophysiological mechanism by which anticoagulant and thrombolytic therapy induces CCE is uncertain. Most authors [15, 18] agree that these medications lyse the platelet–fibrin protective thrombi covering ulcerated atheromatous plaques which may expose atheromatous material to the circulation.

Patients requiring cardiac surgery are at high risk of developing CCE [25, 26]. These patients with an atheromatous aorta are at risk of the main triggering factors, such as left heart catheterization, aortic cannulation and cross-clamping, and anticoagulant therapy before, during and after surgery. Severe central nervous system complications after cardiac surgery, as described in our patients, have been described widely [27]. These complications are usually related to haemodynamic (e.g. severe intraoperative hypotension) or embolic (left ventricular mural thrombus, atrial fibrillation, air embolism) events.

Severe systemic atheromatous embolization after cardiac catheterization has been described during procedures which are often long and difficult, requiring prolonged manipulations and numerous catheter changes within a severely diseased aorta [7, 28]. The sudden occurrence of clinical features seems to be related to massive embolization of atheromatous fragments dislodged by catheters. Therefore, aortic cross-clamping and canulation could be responsible for similar findings. By studying embolic signals with transcranial Doppler during cardiopulmonary bypass for coronary artery revascularization, Barbut and colleagues [29] showed that all patients ($n = 20$) displayed embolic signals. Most have been recorded during removal of aortic cross clamps (34%) and partial occlusion clamps (24%).

In addition to systemic CCE, atheromatous embolization to the distal coronary circulation may complicate CABG, and be responsible for intraoperative myocardial infarction and death, as experienced in patient No. 2. In a series of 4095 CABG, Keon, Heggtveit and Leduc [30] reported nine deaths (0.22%) related to atheromatous embolization into the coronary microcirculation. Moreover, among 175 patients who were re-operated on after a first CABG, four patients (2.29%) died from intraoperative massive myocardial infarction after atheroembolization of the distal coronary circulation. The atheroemboli were deemed to have originated from ulcerative atherosclerotic lesions in the aortic root at the ostia of the coronary arteries or vein grafts, or both, from coronary endarterectomy sites, or from mechanical disruption of plaques in the major epicardial coronary arteries during intraoperative manipulation of the heart. The higher rate of atheromatous embolic complications in patients undergoing repeated CABG is probably related to more severe atherosclerosis with soft mushy atheroma in old vein grafts.

Even though some investigators reported clinical and biological improvements with steroid therapy [1, 8, 31] or pentoxifylline [32], severe systemic CCE has a poor prognosis. The treatment is usually symptomatic, including renal and haemodynamic support.

In patients with severe aortic lesions, transoesophageal echocardiography led surgeons to modify their technique using an alternative cannulation site, hypothermic circulatory arrest [33], exploration and debridement of the aortic arch [34] or resection and graft replacement of the involved aortic segment [35]. Recently, Katz and colleagues [34] studied 130 patients undergoing open heart surgery and examined atherosclerotic lesions in the aortic arch using transoesophageal echocardiography (TOE). The severity of aortic atheromatosis was the only predictor of stroke. Ribakove and colleagues [33] found similar results, demonstrating that intraoperative clinical evaluation of aortic artheromatous disease by surgical palpation alone is not predictive of embolic stroke. Other observations revealed that TOE may demonstrate atheromatous plaques of the aortic arch involved in cholesterol embolization [36, 37] and so detect patients with a high risk of CCE before surgery. Wareing and colleagues [38] have proposed performing ascending aortic replacement or carotid endarterectomy to decrease the stroke rate after cardiac surgery in patients in whom atheromatous plaques were discovered by intraoperative ultrasonic scanning. Other studies [39, 40] have shown that intraoperative echography during cardiac surgery was able to predict patients with a high cerebral complication rate in relation to different stages of atheroma in the ascending aorta.

However, symptoms related to CCE must be sought before CABG: renal insufficiency after left heart catheterization associated with eosinophilia, blue toes syndrome and livedo reticularis. These symptoms indicate the need for a skin or muscular biopsy. Histological confirmation is essential for diagnosis and may help to age the different lesions.

When CCE is confirmed, we believe that CABG is contraindicated because of the poor prognosis of cardiac surgery.

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References

1. McDonell Richards A, Eliot R, Kanjuh V, Bloemendaal RD, Edwards JE. Cholesterol embolism: a multiple-system disease masquerading as polyarteritis nodosa. *American Journal of Cardiology* 1965; **15**: 696–707.
2. Flory CM. Arterial occlusions produced by emboli from eroded aortic atheromatous plaques. *American Journal of Pathology* 1945; 21: 549–565.
3. Snyder H, Shapiro J. A correlative study of atheromatous embolism in human beings and experimental animals. *Surgery* 1961; **49**: 195–204.
4. Ramirez G, O'Neill WM, Lambert R, Bloomer A. Cholesterol embolization: a complication of angiography. *Archives of Internal Medicine* 1978; **138**: 1430–1432.
5. Dahlberg PJ, Frecentese DF, Cogbill TH. Cholesterol embolism: experience with 22 histologically proven cases. *Surgery* 1989; **105**: 737–746.
6. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 2—1991. A 60-year-old woman with hypertension, seizures, and mild renal failure. *New England Journal of Medicine* 1991; **324**: 113–120.
7. Gaines PA, Cumberland DC, Kennedy A, Welsh CL, Moorhead P, Rutley MS. Cholesterol embolisation: a lethal complication of vascular catheterisation. *Lancet* 1988; **1**: 168–170.
8. Drost H, Buis B, Haan D, Hillers JA. Cholesterol embolism as a complication of left heart catheterization. Report of 7 cases. *British Heart Journal* 1984; **52**: 339–342.
9. Colt HG, Begg RJ, Saporito JJ, Cooper WM, Shapiro AP. Cholesterol emboli after cardiac catheterization (8 cases and a review of the literature). *Medicine* 1988; **67**: 389–400.
10. Suc JM, Dumazer P, Bonafe JL, Modesto A. Les embolies systémiques de cristaux de cholestérol. *47ème Congrès Français de Médecine*. Paris: Masson, 1989; 3–29.
11. Fine M, Kapoor W, Falanga V. Cholesterol crystal embolization: a review of 221 cases in the English literature. *Angiology* 1987; **38**: 769–784.
12. Mashiah A, Pasik S, Hurwitz N. Massive atheromatous emboli to both kidneys: a fatal complication following aortic surgery. *Journal of Cardiovascular Surgery* 1988; **29**: 60–62.
13. Feder W, Auerbach R. "Purple toes": an uncommon sequela of oral coumarin drug therapy. *Annals of Internal Medicine* 1961; **55**: 911–917.
14. Hyman BT, Landas SK, Ashman RF, Schelper RL, Robinson RA. Warfarin-related purple toes syndrome and cholesterol microembolization. *American Journal of Medicine* 1987; **82**: 1233–1237.
15. Bruns F, Segel D, Alder S. Control of cholesterol embolization by discontinuation of anticoagulant therapy. *American Journal of Medicine Science* 1978; **275**: 105–108.
16. McGowan J, Greenberg A. Cholesterol atheroembolic renal disease. Report of 3 cases. *American Journal of Nephrology* 1986; **6**: 135–139.
17. Spangen L, Liljeqvist L, Ljungdahl I, Somell A. Temporary changes in renal function following streptokinase therapy: a case report. *Acta Medica Scandinavica* 1976; **199**: 335–336.
18. Rieben FW, Waldherr R, Oster P, Schettler G. Akutes Nierenversagen als Folge diffuser Cholesterinkristall Embolisation unter Streptokinasetherapie. *Deutsche Medizinische Wochenschrift* 1979; **41**: 1447–1449.
19. Schwartz MW, McDonald GB. Cholesterol embolization syndrome: occurrence after intravenous streptokinase therapy for myocardial infarction. *Journal of the American Medical Association* 1987; **258**: 1934–1935.
20. Pochmalicki G, Feldman L, Meunier P, Rougeot C, Weschler J, Jan F. Cholesterol embolisation syndrome after thrombolytic therapy for myocardial infarction [letter] *Lancet* 1992; **339**: 58–59.
21. Bhardwaj M, Goldweit R, Erlebacher J, Kashani M, Levin D, Leber G. Tissue plasminogen activator and cholesterol crystal embolization. *Annals of Internal Medicine* 1989; **111**: 687–688.
22. Queen M, Biem HJ, Moe GW, Sugar L. Development of cholesterol embolization syndrome after intravenous streptokinase for acute myocardial infarction. *American Journal of Cardiology* 1990; **65**: 1042–1043.
23. Ridker PM, Michel T. Streptokinase therapy and cholesterol embolization. *American Medical Journal* 1989; **87**: 357–358.
24. Shapiro LS. Cholesterol embolization after treatment with tissue plasminogen activator. *New England Journal of Medicine* 1989; **321**: 1270.
25. Masuda J, Yutani C, Ogata J, Kuriyama Y, Yamaguchi T. Atheromatous embolism in the brain: a clinicopathologic analysis of 15 autopsy cases. *Neurology* 1994; **44**: 1231–1237.
26. Otsubo H, Kaito K, Takahashi H, Yokoi K, Iwano K, Kaida H, Hashimoto T, Sakai O. Cholesterol emboli following percutaneous transluminal coronary angioplasty as speculated by toe skin biopsy. *Internal Medicine* 1995; **34**: 134–137.
27. Furlan AJ, Breuer AC. Central nervous system complications of open heart surgery. *Stroke* 1984; **5**: 912–915.
28. Harrington D, Amplatz K. Cholesterol embolization and spinal infarction following aortic catheterization. *American Journal of Radiology* 1972; **115**: 171–174.
29. Barbut D, Hinton RB, Szatrowski TP, Hartman GS, Bruefach M, Williams-Russo P, Charlson ME, Gold JP. Cerebral emboli detected during bypass surgery are associated with clamp removal. *Stroke* 1994; **25**: 2398–2402.
30. Keon WJ, Heggtveit HA, Leduc J. Perioperative myocardial infarction caused by atheroembolism. *Journal of Thoracic and Cardiovascular Surgery* 1982; **84**: 849–855.
31. Goldman M, Rickaert F, Voordecker P, Goldman S, Flament-Durand J. Disseminated cholesterol embolism presenting as neuromyelitis optica. *British Medical Journal* 1987; **295**: 697.
32. Carr ME jr, Sanders K, Todd WM. Pain relief and clinical improvement temporally related to the use of pentoxifylline in a patient with documented cholesterol emboli: a case report. *Angiology* 1994; **45**: 65–69.
33. Ribakove GH, Katz ES, Galloway AC, Grossi EA, Esposito RA, Baumann FG, Kronzon I, Spencer FC. Surgical implications of transesophageal echocardiography to grade the atheromatous aortic arch. *Annals of Thoracic Surgery* 1992; **53**: 758–763.
34. Katz ES, Tunick PA, Rusinek H, Ribakove G, Spencer FC, Kronzon I. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. *Journal of the American College of Cardiology* 1992; **20**: 70–77.
35. Kouchoukos NT, Wareing TH, Daily BB, Murphy SF. Management of the severely atherosclerotic aorta during cardiac operations. *Journal of Cardiac Surgery* 1994; **9**: 490–494.
36. Amarenco P, Cohen A, Baudrimont M, Bousser MG. Transesophageal echocardiographic detection of aortic arch disease in patients with cerebral infarction. *Stroke* 1992; **23**: 1005–1009.
37. Sato Y, Takei H, Katsumata N, Matsumoto N, Akiyama H, Narumiya T, Saito F, Kurumatani H, Sakamaki T, Kanmatsuse K. Transesophageal echocardiographically detected atherosclerotic aortic debris in a patient with systemic embolism following coronary angiography. *Heart and Vessels* 1995; **10**: 167–169.
38. Wareing TH, Davila-Roman VG, Daily BB, Murphy SF, Schechtman KB, Barzilai B, Kouchoukos NT. Strategy for the reduction of stroke incidence in cardiac surgical patients. *Annals of Thoracic Surgery* 1993; **55**: 1400–1408.
39. Hosoda Y, Watanabe M, Hirooka Y, Ohse Y, Tanaka A, Watanabe T. Significance of atherosclerotic changes of the ascending aorta during coronary bypass surgery with intraoperative detection by echography. *Journal of Cardiovascular Surgery Torino* 1991; **32**: 301–306.
40. C Davila-Roman VG, Barzilai B, Wareing TH, Murphy SF, Kouchoukos NT. Intraoperative ultrasonographic evaluation of the ascending aorta in 100 consecutive patients undergoing cardiac surgery. *Circulation* 1991; **84** (Suppl: III): 47–53.

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ABSTRACTS

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NOTTINGHAM MEETING

March 28–29, 1996

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Modulation of recombinant invertebrate $GABA_A$ receptors by isoflurane: effects of a point mutation in the M2 domain

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GABA is the most important inhibitory transmitter in the mammalian brain. The $GABA_A$ receptor is an aggregate of 5 subunits which form an integral anion channel. This receptor is modulated at clinical concentrations, by a broad range of anaesthetic drugs [1] which displace radiolabelled probes, like picrotoxinin or *t*-butyl-bicyclo-phosphoro-thionate (TBPS), from a putative site in the ion channel [2]. A point mutation (Fig 1A) in the M2 (transmembrane) helix, which lines an invertebrate chloride channel, confers insensitivity to the $GABA_A$ antagonist, picrotoxinin [3]. We have examined anaesthetic sensitivity of both wild-type (WT) and mutant (Mut) forms of this *Drosophila* RDL subunit.

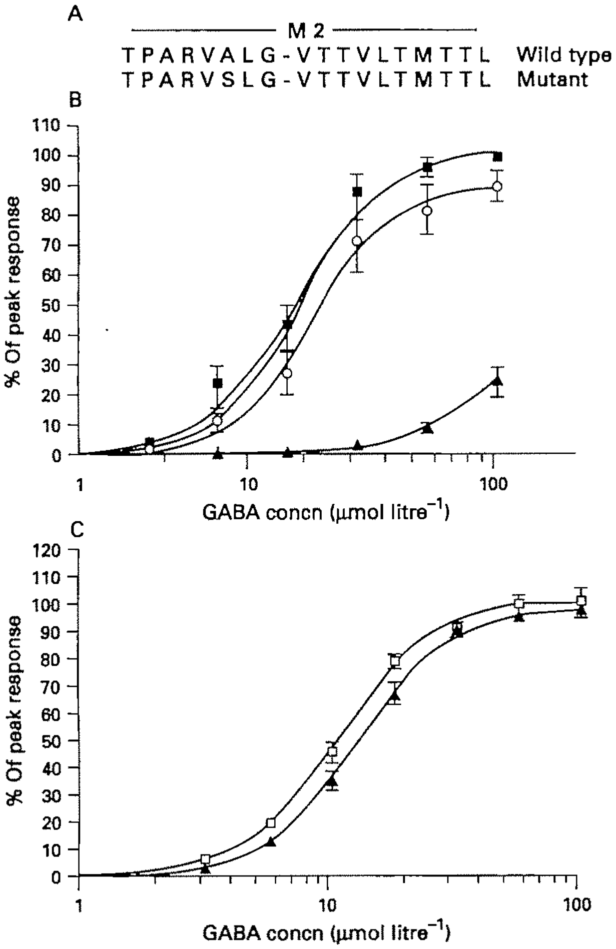

Figure 1 A: Amino-acid single letter code for the m2 region depicting the point mutation (A = alanine, S = serine). B: Effect of picrotoxin 10 μmol litre^{-1}. (■), Before picrotoxin, (○), mutant+picrotoxin, (▲), wild type+picrotoxin ($n = 6$). C: Enhancement of GABA responses by mutant+isoflurane 700 μmol litre (□), and control (▲).

cDNA samples (Cornell University) were transcribed *in vitro*, then expressed in *Xenopus* oocytes using standard techniques [3]. Ion channels were examined 1 to 5 days later using two-electrode voltage-clamp. GABA was applied for 5–15 s by throughput perfusion (approx. 10 ml min^{-1}). Sigmoid log concentration-response curves were fitted by non-linear regression to a three term logistic function before and after equilibration with drugs. Statistical assessment of pharmacological results was by two-tailed Student's *t* test, where appropriate.

WT and Mut currents reversed at −28.4 (SE 0.48; $n = 3$) mV and −28.6 (SE 2.69; $n = 4$) mV, respectively (consistent with a chloride current in the oocyte) and were both absolutely insensitive ($n = 4$/subunit) to 100 μmol litre^{-1} bicuculline ($P > 0.2$). We confirmed the relative insensitivity of the mutant channel to picrotoxin 10 μmol litre^{-1} (Fig 1B: the parallel right shift and depression (by 10%) of the maximal current suggest a "mixed" blocking action.

The point mutation reduced the relative potency of picrotoxin (at the GABA EC_{20}) by about sevenfold. Isoflurane (700 μmol litre^{-1}) reversibly enhanced subsaturating GABA currents by increasing the affinity of GABA for both the WT (not shown) and Mut receptors (Fig 1C). Dose–response curves were shifted left in a parallel fashion. Isoflurane modulated the GABA EC_{50} by 0.85×(95% CI 0.78–0.93) for the WT and 0.82×(0.76–0.88) for the Mut (statistically indistinguishable; $n = 11–13$ for each point on curves).

Isoflurane enhanced chloride currents through a "primitive" invertebrate GABA receptor. A point mutation in the putative ion channel domain did not modify anaesthetic sensitivity.

Key words
Brain, $GABA_A$. Anaesthetics volatile, isoflurane.

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References

1. Tanelian DL, Kosek P, Mody I, MacIver B. *Anesthesiology* 1993; 78: 757–776.
2. Moody EJ, Suzdak PD, Paul SM, Skolnick P. *J. Neurochem.* 1988; 51: 1386–1393.
3. Ffrench-Constant RH, Rocheleau TA, Streichen JC, Chalmers AE. *Nature* 1993; 363: 449–451.

Effect of etomidate on the mass response of cells of cortical lamina V evoked by antidromic activation in the urethane-anaesthetized rat

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Etomidate (Hypnomidate) alters the evoked response of the somatosensory, dorsal column pathway at a site different from that affected by other agents such as urethane, halothane or thiopentone. Unlike these agents, etomidate causes perturbation in evoked behaviour at the level of primary somatosensory cortex (SI) [1], whereas the vast majority of other anaesthetics impair transmission of information through the ventrobasal thalamus [2]. By measuring the antidromically-evoked mass response of cell bodies of cortical lamina V, these experiments attempted to determine where etomidate was effective in modulating the excitability of these cortical output neurons.

Twelve rats (Sheffield strain, 190–210 g) were anaesthetized with urethane 1.25–1.5 g kg^{-1} administered i.p. A stimulating electrode was placed in the pyramidal tract and square wave pulses of 50-μs duration and 100-V amplitude, sufficient to cause supramaximal stimulation, were administered at a frequency of 1 Hz. The surface mass evoked response was recorded via a silver bead electrode placed on the exposed primary somatosensory cortex.

Pyramidal tract stimulation evoked stereotyped surface mass responses: a rapidly rising wave of surface positivity that commenced at a post-stimulus latency of approximately 1 ms, rose to a peak of approximately 2 mV at 2 ms and then decayed rapidly, crossing the initial baseline at approximately 2.8 ms. Results from previous experiments [2] suggest that pyramidal tract stimulation causes the activation only of cell bodies at depths corresponding to anatomical lamina V. It is therefore suggested that the surface mass response results from the synchronous firing of cortical lamina V cells in response to depolarization of their efferent axons.

Administration of increasing doses of etomidate (1, 2, 5, 10, 20 mg kg^{-1} i.p.) had no significant effect on the latency nor the amplitude of the mass response evoked by supramaximal pyramidal tract stimulation.

These results suggest that etomidate, which alters the behaviour of the dorsal column pathway at the level of the cortex, does not cause this alteration by reducing the responsiveness of cells of cortical lamina V. It is suggested, therefore, that the changes caused by etomidate in both the mass cortical evoked response and the evoked response of single cells of the cortical laminae result from an alteration in cortical behaviour at a site upstream of cortical lamina V cell bodies. Further experiments will be directed at investigating the effects of etomidate on the electrical behaviour of cortical cells which have synaptic connections with pyramidal cells of cortical lamina V.

Key words
Anaesthetics i.v., etomidate. Brain, cerebral cortex. Rat.

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References

1. Angel A, Arnott, RH. *Journal of Physiology* 1994; **491.P**: 68P.
2. Angel A. *Experimental Physiology* 1991; **78**: 1–38.

Is glutamate release from rat cerebrocortical slices opioid receptor subtype selective?

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We have previously shown that morphine inhibits glutamate release from rat cerebrocortical slices [1], but there are conflicting reports as to specific subtypes involved [2, 3]. We have therefore examined the effects of the following selective agonists on glutamate release, D-Ala^2, *N*-Me-Phe^4, Gly^5-ol (DAMGO μ), [D-Pen^{2,5}]-enkephalin (DPDPE δ), ICI-199441 (κ) and spiradoline (κ).

Cerebrocortical slices (350 μm) were prepared from female Wistar rats (200–250 g). Immediately after suspension in oxygenated (95% oxygen, 5% carbon dioxide) Krebs buffer pH 7.4, the slices were pipetted into a perfusion chamber as previously described [1]. Slices were perfused at 1 ml min^{-1} for 1 h, 2 ml fractions were then collected for 6 min before a 2 min pulse of 46 mmol litre^{-1} K^+ (S_1). Slices were perfused for a further 30 min in basal Krebs before the second application of K^+ (S_2). DAMGO (1 μmol litre^{-1}), DPDPE (1 μmol litre^{-1}), ICI-199441 (1 μmol litre^{-1}) and spiradoline (1 and 100 μmol litre^{-1}), were applied for 30 min between S_1 and S_2. Glutamate concentrations were measured fluorimetrically [1]. Area under the curves, and the (S_2/S_1) ratios were calculated in order to compare the control and drug-treated slices. Wilcoxon rank sum test was used to compare the control and drug-treated slices.

DAMGO (1 μmol litre^{-1}) produced a 66% inhibition of glutamate release. DPDPE (1 μmol litre^{-1}) and ICI-199441 (1 μmol litre^{-1}) were ineffective. Spiradoline at 1 and 100 μmol litre^{-1} reduced glutamate release by 61% and 90% respectively (table 1).

These data suggest a role for μ and possibly κ agonists in the control of glutamate release and implicate these opioid subtypes as potential targets for neuroprotective therapy.

Key words
Brain, cerebral cortex. Analgesics opioids. Rat.

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References

1. Nicol B, Rowbotham DJ, Lambert DG. *British Journal of Pharmacology* 1996; 117: 293P.
2. Ueda M, Sugimoto K, Oyama T, Kuraishi Y, Satoh M. *Neuropharmacology* 1995; 34(3): 303–308.
3. Hayward NJ, Hitchcott PK, Woodruff GN, McKnight AT. *Analgesia* 1995; 1(4–6): 453–456.

Table 1 Effects of selective opioid agonists on glutamate release. Data are mean (SEM) (n = 6–13)

Opioid (μmol litre^{-1})	Selectivity	S_2/S_1 ratio Control	Drug treated	P value
DAMGO (1)	μ	1.30 (0.34)	0.44 (0.11)	0.028
DPDPE (1)	δ	1.00 (0.19)	0.98 (0.15)	0.889
ICI-199441 (1)	κ	1.03 (0.23)	0.84 (0.25)	0.806
Spiradoline (1)	κ	1.29 (0.26)	0.50 (0.16)	0.028
Spiradoline (100)	κ	0.88 (0.10)	0.08 (0.04)	0.028

Different *in vitro* effects of aqueous or lipid etomidate preparations on neutrophil respiratory burst

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Both propofol and its lipid carrier 10% Intralipid showed a concentration-related inhibition of neutrophil respiratory burst (RB) *in vitro* [1]. Because no statistically significant differences

Table 2 Results (mean (SD)) of the respiratory burst (RB) inhibition (%)

Etomidat-Lipuro	10 µg ml^{-1} (1)	100 µg ml^{-1} (2)
RB inhibition (SD)	83.80 (6.34)	96.93 (1.75)
Hypnomidate	10 µg ml^{-1} (3)	100 µg ml^{-1} (4)
RB inhibition (SD)	1.17 (2.20)	6.34 (4.40)
Intralipid 10%	0.6 µl ml^{-1} (5)	6 µl ml^{-1} (6)
RB inhibition (SD)	5.02 (4.85)	90.60 (4.24)
Lipofundin MCT 10%	0.6 µl ml^{-1} (7)	6 µl ml^{-1} (8)
RB inhibition (SD)	11.3 69.57)	86.80 (7.20)

between 10% Intralipid alone and propofol were found the effect of parenteral lipid solutions remained to be clarified. Since propofol is available only in a lipid carrier preparation we studied the effect of an aqueous (Hypnomidate) and a lipid (Etomidat-Lipuro) etomidate preparation on RB *in vitro*. Additionally, the effects or equivalent concentrations of the lipid carrier solutions of etomidate (Lipofundin MCT) and of propofol (Intralipid 10) alone were studied.

After Ethics Committee approval venous blood was drawn from 20 healthy blood donors. Leucocytes were obtained as supernatant by using 1 g sedimentation. The anaesthetic (10 µg ml^{-1} plasma) [2] and 10-fold anaesthetic plasma concentrations of both etomidate preparations were investigated. Additionally, two different Intralipid concentrations (0.6 and 6 µl ml^{-1}) corresponding to its plasma concentrations with anaesthetic and 10-fold anaesthetic propofol concentrations and the same concentrations of lipofundin were studied. The influence of these drugs on RB was measured via flow cytometry by the intracellular oxidation of dihydrorhodamine-123 to the fluorescent rhodamine-123 [3]. The percentage inhibition was calculated in comparison with the positive control response (RB after full stimulation by phorbol myristate acetate in the absence of the tested drugs). Prestimulation of neutrophils was quantified by negative controls (RB without stimulation by phorbol myristate acetate and without drugs). Propidium-iodide viability discrimination was also carried out. Student's *t*- or Wilcoxon test were applied for the evaluation of differences ($P < 0.05$).

The results are presented in table 2. The statistically significant differences are as follows: (1) *vs* (2) ($P < 0.05$), (1) *vs* (3) ($P < 0.001$), (2) *vs* (4) ($P < 0.001$), (5) *vs* (6) ($P < 0.001$), (5) *vs* (7) ($P < 0.05$), (7) *vs* (8) ($P < 0.001$).

In contrast with the lipid preparation, the aqueous etomidate preparation showed an almost irrelevant and not significantly dose-related RB inhibition. Thus the significant effect of the lipid preparation may be due to the lipid carrier alone. Equivalent concentrations of different lipid solutions seem to suppress phorbol myristate acetate stimulated RB by a similar magnitude.

Key words
Anaesthetics, i.v., etomidate.

References

1. Leuwer M, Heine JF, Arseniev L, Scheinichen D, Jaeger K, Piepenbrock S. *British Journal of Anaesthesia* 1996; **76**: 585P.
2. Devlin EG, Clarke RSJ, Mirakhur RK, McNeill. *British Journal of Anaesthesia* 1994; **73**: 315–317.
3. Rothe G, Oser A, Valet G. *Naturwissenschaften* 1988; **75**: 354–355.

Onset of neuromuscular block at the larynx using video imaging

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The onset of neuromuscular block at the larynx has been described previously by Donati and co-workers who measured pressure generated in the cuff of a tracheal tube placed between the vocal cords on superficial stimulation of the recurrent laryngeal nerve [1]. We used video imaging to assess the onset of neuromuscular block at the vocal cords and compared this with the onset of block at the adductor pollicis.

Fourteen (ASA I or II) patients scheduled to undergo elective ENT surgery were recruited. None received premedication and anaesthesia was induced with propofol 2–3 mg kg^{-1} supplemented with alfentanil 10 µg kg^{-1} and maintained with a propofol infusion at 10–12 mg kg^{-1} h^{-1} for the duration of the study period. The patients were allowed to breathe oxygen spontaneously via a laryngeal mask until they became apnoeic when ventilation was supported manually. The left arm was secured for neuromuscular monitoring and an accelerometer (Tof-guard, Biometer, Odense, Denmark) was attached to the wrist. An Olympus P3 fibre-optic scope was introduced via the laryngeal mask and the cords visualized. The recurrent laryngeal nerve was stimulated using a previously described technique [1]. The first seven patients (group 1) received a train-of-four stimulus at 15-s intervals and the subsequent seven (group 2) a single stimulus at 10-s intervals. The movement of the vocal cords to stimuli at 50, 55 and 60 mA was determined and a 60 mA stimulus was applied to the recurrent laryngeal nerve for the remainder of the study. Vecuronium 0.1 mg kg^{-1} was then administered via the i.v. cannula and the responses of the vocal cords to stimulation were recorded on a video tape and the thumb twitch height was stored by the accelerometer. The video tape images were later digitized and the angle between the cords was measured (SigmaScan for Windows, Jandel Scientific) at rest and at the point of maximal contraction until cord movement ceased. The degree of block at the hand and larynx was compared at each time interval using ANOVA and Student's *t*-test.

Table 3 Time to onset of maximal block at the hand and larynx (s) in the two groups

	Train-of-four		Single twitch	
Patient	Hand	Larynx	Hand	Larynx
1	150	165	130	140
2	165	180	290	240
3	135	150	180	210
4	105	165	160	150
5	165	135	130	160
6	210	225	190	110
7	120	135	190	210

There was no difference in the mean time to onset of maximum block at the larynx and the hand using single twitch or train-of-four responses (table 3). The technique did reveal a difference in the change in depression of T1 in the train-of-four group at the larynx and hand during onset of paralysis.

Our findings suggest that video imaging is a useful technique for determining the onset of neuromuscular block at the larynx.

Key words
Neuromuscular block, measurement of response. Neuromuscular block, vecuronium. Monitoring techniques, accelerometry.

Acknowledgements

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Reference

1. Donati F, Plaud B, Meistelman C. *Anesthesiology* 1991; **74**: 827–832.

Contractures of malignant hyperthermia muscle: where do halothane and caffeine act?

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Although the sarcoplasmic reticulum (SR) calcium release channel (ryanodine receptor) is a candidate for a causative defect in malignant hyperthermia (MH), approximately 50% of pedigrees do not show linkage to the relevant gene locus. The crucial role of extracellular calcium and the effects of dihydropyridine agonist and antagonists on the *in vitro* contracture test (IVCT) provide evidence for an effect at the sarcolemma [1]. To examine this further we compared the effects of halothane and caffeine on an intact strip of cut muscle fibres with their effects on the same strip mechanically skinned. Mechanical skinning removes the sarcolemma as an effective barrier and allows free access of solutes to the SR.

Strips of muscle consisting of approximately 50–100 fibres (0.5–1 × 15 mm) were dissected under an inverted microscope. These were mounted horizontally between two clamps in a bathing chamber filled with Krebs solution at room temperature. One clamp was connected via a force transducer to a recorder, the other to a micro-manipulator. The muscle strip was stretched until an increase in tension was first noted and then a further 20 % of this length. The tension changes were recorded while visualizing the reactions to either 2 % halothane or increasing concentrations of caffeine (0.5, 1, 2, 4, 8, 16 and 32 mmol litre^{-1}) in either Krebs solution or a depolarizing solution. The muscle strip was then skinned mechanically by gentle scraping and the tension changes recorded in response to the same drug applied in a solution mimicking intracellular composition. In separate experiments, caffeine or halothane were applied in calcium-free solutions to intact muscle strips. The MH status of each patient was determined using separate IVCTs for caffeine and halothane [2].

The increase in tension of the intact muscle strips correlated with the result of the IVCT for caffeine in Krebs: Spearman correlation coefficient $r = 0.66$, $P = 0.009$, $n = 15$ or in the depolarizing solution $r = 0.69$, $P = < 0.001$, $n = 29$. With halothane in Krebs, the response concurred with the IVCT in 24 of 29 experiments, Cohen's kappa = 0.62 and with halothane in the depolarising solutions in 27 of 33 experiments, Cohen's kappa 0.74. In 12 intact strip preparations from MH susceptible individuals, 2 % halothane in the absence of calcium did not increase tension. In only two of 11 intact strip preparations did caffeine in the absence of calcium cause an increase in tension, and this occurred at four times the caffeine concentration that produced an increase in tension in the presence of calcium. In the mechanically skinned preparations the increase in tension induced by caffeine occurred at lower caffeine concentrations and did not correlate with the IVCT result; Spearman correlation coefficient $r = 0.15$, $P = 0.12$, $n = 15$. The first 33 mechanically skinned preparations exposed to 2 % halothane all produced increases in tension (14 MH susceptible, 19 MH normal).

The IVCT seems to reflect calcium movement across the sarcolemma. We could not distinguish between MH susceptible and normal muscle at the level of the SR.

Key words
Complications, malignant hyperthermia. Muscle, skeletal.

References

1. Adnet PJ, Krivosic-Horber RM, Adamantidis M, Reyford H, Cordonnier C, Houdecoeur. *Anesthesiology* 1991; 75: 413–419.
2. European Malignant Hyperpyrexia Group. *British Journal of Anaesthesia* 1984; 56: 1267–1269.

Hyaluronidase and peribulbar block

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Peribulbar block provides good quality local anaesthesia for intraocular surgery. Hyaluronidase improves the speed of onset and quality of retrobulbar block [1], but its role in peribulbar block has been questioned [2]. We present the preliminary findings of a randomized study investigating the effects of two concentrations of hyaluronidase on peribulbar block.

A total of 198 patients undergoing elective intraocular surgery were allocated randomly to one of three groups. Group 1 ($n = 50$), control) received a peribulbar block using 5 ml of a 1:1 mixture of 0.5 % bupivacaine and 2 % lignocaine. Group 2 ($n = 74$) received this solution supplemented with hyaluronidase 50 iu ml^{-1}. Group 3 ($n = 74$) received the same solution supplemented with hyaluronidase 300 iu ml^{-1}. All blocks were performed by the same investigator using the technique described by Apel and Woodward [3]. Reduction in ocular motility was considered the only reliable sign of successful block and movement of the superior, inferior, medial and lateral recti were scored as follows: normal movement = 2, reduced movement = 1 and akinesia = 0. The block was assessed at 1, 5 and 10-min intervals and a score of 4 or less or reduced movement in all directions was taken to indicate a successful block. A supplementary injection of 2 % lignocaine 3 ml was given if the block was unsatisfactory at 5 min. Further assessment was performed at 5-min intervals. The total volume of local anaesthetic required was recorded. Demographic data were analysed using ANOVA, while ocular motility scores and total volume of local anaesthetic required were compared using chi-square tests.

Table 4 Successful blocks at 5 min. $*P < 0.05$, $***P < 0.001$ compared with control

	Successful block (%)	Unsuccessful block (%)
Control	33 (66)	17 (34)
Hyaluronidase (50 iu)	62 (84)*	12 (16)
Hyaluronidase (300 iu)	67 (91)***	7 (9)

The groups were comparable for age, sex and ASA status. At 1 min, ocular motility scores were significantly lower in group 3 compared with control ($P < 0.05$). The incidence of satisfactory block at 5 min was increased in both groups given hyaluronidase (group 2 $P < 0.05$; group 3 $P < 0.001$) (table 4). There was no statistically significant differences between the number of patients in groups 2 and 3 with satisfactory blocks at 5 min. If a satisfactory block was achieved at 5 min then the 10-min score was omitted. By 10 min, all but two patients had satisfactory blocks. Four patients in the control group had clinical evidence of a sustained increase in intraocular pressure, necessitating, in one instance, cancellation of surgery.

Hyaluronidase 300 iu improves the speed of onset of peribulbar block. Hyaluronidase at both concentrations improves the quality of peribulbar anaesthesia at 5 min after injection. The study will continue in order to determine the optimal concentration of hyaluronidase to use with this technique.

Key words
Surgery, ophthalmological. Anaesthetics local. Enzymes, hyaluronidase.

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References

1. Thompson I. *British Journal of Ophthalmology* 1988; 72: 700–702.
2. Brydon CW, Basler M, Kerr WJ. *Anaesthesia* 1995; 50: 998–1000.
3. Apel A, Woodward R. *Australian and New Zealand Journal of Ophthalmology* 1991; 19(2): 149–153.

The Deltatrac metabolic monitor for measuring oxygen consumption during orthotopic liver transplantation

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Oxygen consumption ($\dot{V}O_2$) increases after reperfusion during orthotopic liver transplantation (OLT). The magnitude of the change may reflect liver oxygen uptake and have useful prognostic value for graft function [1]. The reliability of the reverse Fick method has been questioned recently and this has renewed interest in alternative methods of measuring $\dot{V}O_2$. The Deltatrac metabolic monitor (Datex, Helsinki) calculates $\dot{V}O_2$ by measuring carbon dioxide elimination ($\dot{V}CO_2$) and deriving the respiratory quotient (RQ) from inspired and expired oxygen and carbon dioxide fractions [2]. The assumption is made that a steady state is present and that $\dot{V}CO_2$ results only from metabolic production. $\dot{V}O_2$ is calculated as $\dot{V}CO_2$/RQ. This study was designed to examine when this assumption is valid after reperfusion.

Twenty patients undergoing OLT were studied 30 min before, 30 min after, and 90 min after reperfusion. At each time point an arterial blood gas was taken and 5-min averages calculated from Deltatrac recordings for $\dot{V}O_2I$, $\dot{V}CO_2I$, RQ, and mixed expired

Table 5 Results. Column (2) *vs* (1) ***$P < 0.001$, *$P < 0.02$; column (3) *vs* (2) †††$P < 0.001$, †$P < 0.02$. Other changes NS

	(1) Before reperfusion Mean (SD)	(2) 30 min after reperfusion Mean (SD)	(3) 90 min after reperfusion Mean (SD)
$\dot{V}CO_2I$ (ml min^{-1} m^{-2})	80 (15)	103 (19)***	111 (19)†††
RQ	0.87 (0.12)	0.82 (0.10)*	0.83 (0.10)
$\dot{V}O_2I$ (ml min^{-1} m^{-2})	93 (15)	126 (23)***	134 (23)†
Pa_{CO_2} (kPa)	4.40 (0.73)	5.27 (0.90)***	5.47 (0.70)
H^+ (nmol litre^{-1})	44.80 (9.62)	52.85 (9.95)***	50.21 (9.01)
St.HCO_3^- (mmol litre^{-1})	20.84 (2.95)	19.88 (2.42)*	21.27 (2.73)†††
V_D/V_T	0.49 (0.06)	0.46 (0.09)*	0.44 (0.09)
CI (litre min^{-1} m^{-2})	4.58 (1.38)	5.87 (1.56)***	6.26 (1.53)

carbon-dioxide fraction (FE_{CO_2}). Pulmonary deadspace ratio was calculated from the Bohr equation. Cardiac index (CI, Baxter Vigilance) was recorded at each study point. Ventilation and FI_{O_2} were not changed during the study period. A total i.v. anaesthetic technique was employed. Statistical analysis was by paired Student's *t*-test.

We attempted to identify and measure factors which influence $\dot{V}CO_2$ other than metabolic production. These include acid-base disturbances, acute changes in lung perfusion and pulmonary deadspace changes. At 30 min after reperfusion an increase in Pa_{CO_2} occurred in association with acute metabolic acidosis as a result of acid washout from the graft and from previously ischaemic tissues. The acute increase in cardiac output and decrease in pulmonary deadspace are consistent with an increase in alveolar perfusion.

Together, these factors will increase $\dot{V}CO_2$ above metabolic production until a new steady state is established. Calculated $\dot{V}O_2$ at this time will be subject to inaccuracy. Between 30 and 90 min no significant changes occurred in Pa_{CO_2}, RQ, V_D/V_T and CI. Standard bicarbonate increased significantly and it is unlikely that continuing acid washout from the graft and splanchnic circulation is contributing to the increase in $\dot{V}CO_2$ at this time. Hydrogen ion concentration remained elevated because ventilation was kept constant throughout the study period. Carbon dioxide stores in the body are large and exist in multiple compartments. It remains possible that $\dot{V}CO_2$ is affected by factors other than metabolic production at 90 min after reperfusion but the resulting error in $\dot{V}O_2$ is likely to be small (table 5).

The measurement of $\dot{V}O_2$ with the Deltatrac metabolic monitor is not straightforward during OLT. Factors other than metabolic production can alter carbon dioxide elimination and should be evaluated when the Deltatrac metabolic monitor is used to estimate $\dot{V}O_2$.

Key words
Surgery, transplantation. Surgery, hepatic. Oxygen, measurement.

References

1. Steltzer H, Hiesmayr M, Tuchy G, Zimpfer M. *Anesthesia and Analgesia* 1993; **76**: 574–579.
2. Makita K, Nunn JF, Royston B. *Critical Care Medicine* 1990; **18**: 638–644.

Use of the Bland and Altman statistical method in the anaesthesia literature

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Many statistical tests including correlation and regression, are used to compare two methods of clinical measurement. Since 1976, Feinstein [1] reported his concern regarding an author's choice of test. These tests may show an association but do not necessarily support the substitution of one method of measurement for the other. In 1983, Bland and Altman proposed a different way of comparing two methods of clinical measurement [2]. The data should be represented by plotting the difference of two values against the mean. Bias refers to the mean difference while limits of agreement refers to the standard deviation of the mean. This method was further reported in the medical literature in 1986 [3].

We have assessed the use of the Bland and Altman statistical method in the anaesthesia literature. The journals *Anaesthesia, British Journal of Anaesthesia, Canadian Journal of Anaesthesia, Anaesthesia and Intensive Care, Anesthesia & Analgesia* and *Anesthesiology* were chosen. We reviewed by page the original articles from 1 January 1990 to 31 December 1994 and selected the papers reporting a comparison of two or more methods of clinical measurement. Overall, in 1990 six of 26 (23%) original articles used Bland and Altman. The proportion increased to 20 of 30 (66%) during the following year. This figure remained similar from 1992 to 1994 (1992, 10 of 16 (62%), in 1993, 17 of 28 (60%), and 1994, 16 of 26 (61%)).

The type of clinical measurements are associated with the type of statistical test. Thirty one studies compared different methods of measuring cardiac output, and 25 (80%) used Bland and Altman. Fourteen of 23 (60%) articles comparing methods of assessing non-invasive blood pressure measurement used Bland and Altman. A similar proportion, 21 of 33 (63%), was observed for methods measuring blood gases or oxygen saturation. These contrast with the smaller number of papers choosing Bland and Altman to test the relationship between methods of measuring non-invasive end-tidal carbon dioxide (10%) and body temperature (33%). In those original papers where Bland and Altman was not used, data were analysed by regression and/or correlation in 37 articles, *t*-test in 11, ANOVA in four articles and no statistics in five. Despite the success of the Bland and Altman method [3] with over 1500 citations by July 1994, correlation and/or regression are still widely used for the comparison of two methods of clinical measurement in the anaesthesia literature.

Key words
Statistics.

References

1. Feinstein AR. *Clinical Pharmacology and Therapeutics* 1976; **20**: 617–631.
2. Altman DG, Bland JM. *Statistician* 1983; **32**: 307–317.
3. Bland JM, Altman DG. *Lancet* 1986; **8**: 307–310.

Cerebral blood flow and metabolic rate for oxygen after acute brain injury, managed with induced arterial hypertension

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Advances in the medical treatment of patients with severe brain injury depend upon a better understanding of the pathophysiology including biochemical and blood flow abnormalities that occur after injury. The management of such patients has evolved from an intracranial pressure (ICP) to an arterial pressure (AP)-orientated approach to cerebral perfusion pressure management (CPP) [1]. We report cerebral blood flow (CBF) measurements in

Table 6 Measured variables and calculated variables (median, range)

Variable		Median	Range
CPP	(mm Hg)	72	57–119
CBF	(ml 100 g min^{-1})	90	24.3–441
Pa_{CO_2}	(kPa)	3.91	3.49–4.59
Sj_{O_2}	(%)	67	52–83
$CMRo_2$	(ml oxygen 100 g min^{-1})	4.28	0.45–48.54
MFV	(cm s^{-1})	102	49–160

this patient population with induced arterial hypertension (table 6).

All patients were managed according to a standard procedure that included intubation, ventilation, sedation (alfentanil 0.02 mg kg^{-1} h^{-1} and midazolam 0.07 mg kg^{-1} h^{-1}) and, if necessary, paralysis with atracurium. ICP (Camino transducer), arterial blood pressure, body temperature and jugular venous saturation (Baxter Health Care) were recorded continuously. Therapeutic goals were a CPP of > 70 mm Hg, achieved using noradrenaline infusion (4 μg kg^{-1} h^{-1}); Pa_{CO_2} 4–5 kPa and cerebral venous oxygen saturation of > 50%; manipulated by optimizing CPP and Pa_{CO_2}.

Cerebral blood flow was measured between day 0 and 3 in intensive care, using the nitrous oxide saturation method [2]. Mean blood flow velocity (MFV) in the middle cerebral artery was measured by transcranial Doppler sonography (TCD 2000 EME, Germany).

Seventeen patients were studied on 34 occasions in the intensive care unit after severe brain injury (8 = traumatic head injury; 9 = subarachnoid haemorrhage). All the measures were made when cerebral perfusion pressure (CPP = mean arterial pressure-intracranial pressure) was greater than 57 mm Hg and jugular saturation of oxygen and Pa_{CO_2} within normal limits.

Cerebral blood flow measured in this patient population is greater than previously reported. These results may reflect the effect of inotrope therapy or be due to the limitations of the CBF measurement technique.

Key words

Brain, blood flow. Brain, perfusion pressure.

References

1. Jones PA, Andrews PJD, Migdley S, Anderson SI, Piper IR, Tocher JL, Housley AM, Corrie JA, Slattery J, Dearden NM, Miller JD. *Journal of Neurosurgical Anesthesiology* 1994; 6: 4–14.
2. Kety SS, Schmidt CF. *American Journal of Physiology* 1945; 143: 53–66.

Decreased arterial oxygenation during deliberate hypotension: a comparison of trimetaphan camsylate, sodium nitroprusside and glyceryl trinitrate

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Hypotensive agents may impair pulmonary gas exchange. The effects of trimetaphan camsylate on gas exchange in humans have not yet been fully documented. The aim of this crossover trial was to disclose any differences between the effects of trimetaphan, sodium nitroprusside and glyceryl trinitrate on arterial oxygenation in humans.

Twelve patients were studied, whose lungs were mechanically ventilated following elective coronary artery surgery. Trimetaphan, sodium nitroprusside and glyceryl trinitrate were given to each patient in random succession, aiming for a 20% decrease in mean arterial pressure. Before, during and after infusion of each drug cardiac index (CI), mean pulmonary artery pressure (MPAP), arterial oxygen tension (Pa_{O_2}), mixed venous oxygen saturation (Sv_{O_2}) and shunt fraction (Q_s/Q_t) were determined. Statistical analysis was by two-way analysis of variance.

Trimetaphan decreased cardiac index. All three drugs reduced MPAP, Pa_{O_2} and Sv_{O_2}. Trimetaphan lowered Pa_{O_2} to a lesser extent than did the other two drugs. Both sodium nitroprusside and glyceryl trinitrate increased venous admixture, whereas trimetaphan did not (table 7).

Table 7 Haemodynamic and gas exchange variables before and during a 20% reduction in arterial pressure induced with trimetaphan camsylate (TC), sodium nitroprusside (SNP) and glyceryl trinitrate (GTN). (lsd least significant difference, $P = 0.01$; * = $P < 0.02$ compared with baseline)

	TC	SNP	GTN	lsd
CI (litre min^{-1} m^{-2})				
Baseline	3.73	3.68	3.36	0.47
Hypotension	3.26*	3.80	3.35	
MPAP (mm Hg)				
Baseline	18.0	19.2	18.2	1.7
Hypotension	14.4*	15.3*	14.3*	
Pa_{O_2} (kPa)				
Baseline	16.30	17.42	17.38	1.59
Hypotension	14.87*	12.31*	13.39*	
Sv_{O_2} (%)				
Baseline	74.4	74.3	73.0	2.6
Hypotension	71.3*	71.3*	70.1*	
Q_s/Q_t				
Baseline	0.159	0.145	0.144	0.030
Hypotension	0.158	0.192*	0.184*	

Three possible mechanisms have been postulated to explain a decrease in Pa_{O_2} during deliberate hypotension [1]: first, a reduction in cardiac output and thus mixed venous oxygen content; second, redistribution of blood flow to dependent lung regions as a consequence of pulmonary arterial hypotension; third, inhibition of hypoxic pulmonary vasoconstriction (HPV). In this study trimetaphan decreased Pa_{O_2} by reducing cardiac output. Sodium nitroprusside and glyceryl trinitrate seemed to impair gas exchange by blunting HPV.

Key words

Lung, gas exchange. Complications, hypotension.

References

1. D'Oliveira M, Sykes MK, Chakrabarti MK, Orchard C, Keslin J. *British Journal of Anaesthesia* 1981; 53: 11–17.

Assessment of a model predicted infusion of ketamine used with propofol for total i.v. anaesthesia

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Ketamine may be used in low doses to provide analgesia [1] with little respiratory depression [2] and may therefore be used to augment propofol anaesthesia in spontaneously breathing patients. The aim of this study was to assess the predictive performance and clinical suitability of a ketamine model predicted infusion (MPI) system, used for total i.v. anaesthesia with propofol. This used a computer programmed with ketamine pharmacokinetics [3] and patient weight to control a Graseby 3400 infusion pump. Computer-predicted blood concentrations were compared with concentrations measured by gas-liquid chromatography [2].

Nineteen patients (13 male) of ASA grade I and II, aged 18 to 80 yr within 20% of ideal body weight entered the study. Patients were premedicated with temazepam 20 mg 1 h before surgery. After pre-oxygenation a predicted concentration between 200 and 300 ng ml^{-1} was selected and the infusion started. On reaching the predicted concentration propofol was given to achieve loss of verbal contact. The propofol infusion continued at 10 mg kg^{-1} h^{-1} and was adjusted subsequently as required. A laryngeal mask airway was sited and the patient breathed an air/oxygen mixture to maintain an Sp_{O_2} greater than 95%. After the start of the operation the ketamine concentration was adjusted as clinically indicated. Blood ketamine concentrations were measured before starting the infusion, 5 min later, immediately before the start of the procedure, immediately before an increase in concentration, 3 and 5 min later; immediately before a decrease in concentration, on reaching it and 5 min later; before terminating the infusion, 5 and 10 min later.

The performance error was calculated for each sampling point and the median predictive error (MDPE) and median absolute predictive error (MDAPE) were calculated for each patient and the population as a whole. The model gave effective control of blood ketamine concentrations; MDPE 18.7 (range −12 to 60.7) and MDAPE 22.7 (range 8.9 to 60.7). The technique provided good clinical anaesthesia with mean propofol and ketamine doses of 9.3 and 0.94 mg kg^{-1} h^{-1} respectively. The predicted ketamine concentration ranged from 200 to 500 ng ml^{-1} during maintenance. Six patients had apnoea at induction, but subsequently respiratory depression did not occur, with a mean end-tidal carbon dioxide of 5.9 kPa during maintenance. Mean time (range) to eye opening after terminating the infusions was 13.3 (4–25) min. No patients described unpleasant dreams or hallucinations.

Key words

Anaesthetics i.v., ketamine. Drug delivery, computerized.

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References

1. Clements JA, Nimmo WS. *British Journal of Anaesthesia* 1981; **53**: 27–30.
2. Soliman MG, Brindle GF, Kuster G. *Canadian Anaesthetic Society Journal* 1975; **22**: 486–94.
3. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. *Anaesthetist* 1975; **24**: 260–3.

Pharmacokinetics of tenoxicam administered by i.v. or i.v. regional routes

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Tenoxicam is an oxicam non-steroidal anti-inflammatory drug (NSAID) available for i.v. use. Pharmacokinetic data from healthy volunteers and patients with chronic musculoskeletal disorders suggest it has an elimination half-life in excess of 30 h [1]. The kinetics of this drug have not previously been described in patients after operation. There is work suggesting that NSAIDs given into an isolated limb as part of an i.v. regional anaesthetic technique reduce both intraoperative tourniquet pain and postoperative pain [2]. We have investigated the pharmacokinetics of tenoxicam given by both i.v. (IV) and i.v. regional (IVR) routes.

Ten patients undergoing open fixation of an ankle fracture were assigned randomly to receive tenoxicam 20 mg (diluted to a volume of 60 ml with 0.9% saline) either as an i.v. injection after induction of anaesthesia ($n = 5$) or injected into a cannulated vein in the fractured foot after limb exsanguination and inflation of a thigh tourniquet ($n = 5$). Baseline blood samples were taken from a dedicated venous cannula immediately before drug injection (IV group) and during the period of tourniquet inflation (IVR group). Further blood samples were taken at 0.5, 2, 5, 10, 20, 30, 60, 120, 240, 360 min and 24 h after drug injection (IV group) or tourniquet deflation (IVR group). Samples were centrifuged and the plasma stored at −70 °C. Plasma tenoxicam concentrations were measured in duplicate for each sample using high performance liquid chromatography [3]. Pharmacokinetic data were derived from the concentration/time curves using non-linear regression analysis (sum of least squares) and the trapezoidal rule. Concentrations were compared using the Mann–Whitney *U*-test.

There was no systemic leak of tenoxicam (IVR group) during the period of tourniquet inflation. The results for the IV group (but not the IVR group) are described by a tri-exponential decay. Peak plasma concentration in the IVR group was lower and occurred later than in the IV group ($P < 0.05$). After 10 min there was no significant difference in plasma concentration between the two groups. Area under the curve (AUC) analysis showed no difference between the two groups, and estimated the bioavailability in the IVR groups to be 99.5%.

The derived pharmacokinetic variables for the IV group are consistent with previously published data from healthy volunteers. The pharmacokinetic data appear to show that little tenoxicam was retained in the limb when given by an i.v. regional route (table 8).

Table 8 Pharmacokinetic data for the IV and IVR groups (*$P < 0.05$)

	Peak concn (mg $litre^{-1}$)		Time to peak concn (min)		AUC_{24} (mg min $litre^{-1}$)	
	Median	Range	Median	Range	Median	Range
IV group	8.55*	5.6–9.2	0.5	—	2770	2617–3798
IVR group	3.53	2.3–4.4	5.0	0.5–10	3028	1986–4184

Key words

Pharmacokinetics, tenoxicam.

References

1. Nilsen OG. *Clinical Pharmacokinetics* 1994; **26**(1): 16–43.
2. Reuben SS, Steinberg RB, Kreitzer JM, Duprat KM. *Anesthesia and Analgesia* 1995; **81**: 110–113.
3. Mason JL, Hobbs GJ. *Journal of Chromatography* 1995; **665**: 410–415.

Preliminary study of prediction of ICU mortality by artificial neural network

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Artificial neural networks (ANN) are mathematical non-linear models which can be used for the classification of data or multiple non-linear regression [1]. They learn to estimate unknown output values from known training data and can mix parametric and non-parametric data.

The highest, lowest and initial data in the first 24 h from 800 ICU admissions from the John Radcliffe Hospital, Oxford were used for the study. In addition to the normal data used to calculate APACHE II this data set was treated to give the time between hospital and ICU admission (care delay) and the differences between the raw physiological data values and the mid-points of the APACHE II APS score ranges (difference data). Sex, weight and the time for which the primary illness had been present was also included.

The data set was randomly divided into a training and test data set in the ratio of 7:3. Eight cascade correlation multilayer perceptron classifiers were trained using Neural Works PREDICT software. This software automatically examines the input data to find suitable input data transformations for each of the inputs. It also contains a genetic algorithm that examines the data for the minimum subset of inputs consistent with optimum network performance. Data can be excluded or included under manual control as well as being automatically included or excluded by the genetic algorithm search.

ANN were trained using difference and raw data (ANN A), two nets using raw data only (B, C), difference data only (D), all the available data without any automatic selection of inputs at all (E), a minimum set of inputs repeatedly selected by the genetic algorithm search (F), a more extensive set selected by the software (G) and a network where the chronic health information was forced into the input data set (H). The performance of the networks was then tested using the unseen data. For comparison the APACHE II prediction for the test data was also calculated [2]. The risk value was set to give the same proportion of deaths as in the original data set ($R = 0.3$) (table 9).

The variables selected by the generic algorithm varied considerably between networks, probably indicating that there was insufficient data for optimal training of the networks. The complexity of the networks produced suggests that about 2500 cases would be needed for training and testing of a full ANN

Table 9 Performance of classification methods on unseen test data

ANN	Sensitivity %	Specificity %	Correct class %	False +ve %	False −ve %
A	80.00	81.28	81.14	18.72	16.67
B	72.91	88.00	74.56	27.09	24.12
C	76.74	84.37	83.51	15.63	13.87
D	76.00	76.85	76.75	23.15	20.61
E	65.12	89.97	87.17	10.03	8.90
F	88.00	79.8	80.7	20.2	17.98
G	64.00	84.73	82.46	15.27	13.60
H	84.62	94.98	94.49	5.02	4.78
APACHE II	49.00	94.86	89.14	5.14	4.50

solution [3]. Age, care delay, postoperative status, sex, and Glasgow Coma Score were the variables most often selected by the genetic algorithm. The physiological measurements selected varied but were spread fairly uniformly across the APACHE II set. Chronic Health Status was virtually never selected. When forced uniformly into the training of ANN H it seems to have produced an improvement in the network performance.

Key words
Computers, APACHE II. Computers, neural networks.

References

1. DTI Best Practice Guidelines for Neural Network Applications 1994 DTI, London.
2. Knaus WA, Draper EA, Wagner DP, Zimmerman JE *Critical Care Medicine* 1985; **13**: 818–829.
3. Errington PA *PhD Thesis*. University of Manchester, 1995.

Effect of an upper respiratory tract infection on upper airway reactivity

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Many patients presenting for elective surgery will either be suffering with or recovering from a recent upper respiratory tract infection (URTI). The decision whether or not to anaesthetize such a patient is an enduring clinical dilemma, as there is an increased risk of respiratory complications including laryngospasm [1]. By measuring the threshold concentration of ammonia vapour (NH_3TR) required to elicit reflex glottic closure [2], we aimed to determine whether upper airway reflex sensitivity (UARS) changes during the course of an URTI, how long these changes might persist and whether they are related to the presence of symptoms.

Twelve volunteers were recruited 24–72 h after symptoms of an URTI began. We defined URTI as the presence of nasal and throat symptoms, in addition to general malaise. All volunteers were non-smokers, on no medication and gave no history of asthma or URTI in the previous 3 months. Over the next 8 weeks repeated measures of NH_3TR were made, and symptoms were recorded. Measurements were made on the following days (±24 h) after the commencement of symptoms; 3, 6, 9, 15, 20, 27 and 56.

Eleven subjects (six male), mean age 39.8 (range 30–58) yr, completed the study. One subject was asymptomatic at day 6, 5 at day 9 and 10 at day 15. All were asymptomatic by 20 days, and remained so until the study ended at day 56.

Upper airway reactivity as measured by this technique is increased during an URTI. The changes appear to return to normal by day 15 by which time 10 of the 11 subjects were asymptomatic (fig. 2).

Key words
Airway, reflexes. Complications, respiratory.

References

1. Cohen MM, Cameron CB. *Anesthesia and Analgesia* 1991; **72**: 282–288.
2. Langton JA, Murphy PJ, Barker P, Key A, Smith G. *British Journal of Anaesthesia* 1993; **70**: 126–130.

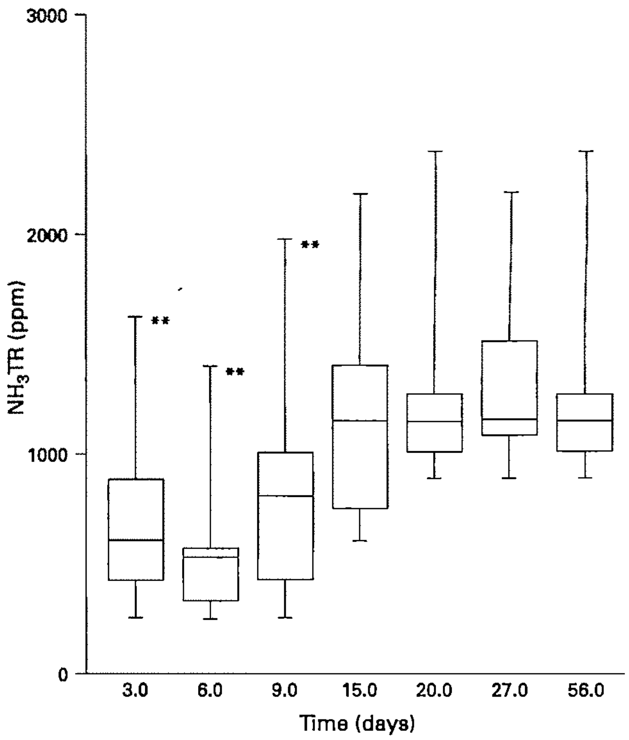

Figure 2 Ammonia threshold concentration (NH_3TR) in volunteers with URTI showing the median, interquartile range and 10th and 90th percentiles. $^{**}P < 0.01$ (Wilcoxon and Mann–Whitney *U* test).

A fibreoptically guided exchange bougie

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The laryngeal mask airway (LMA) has been advocated for use after difficult and failed intubation [1] and as a guide to visualize the larynx with a fibreoptic laryngoscope (FOL) [2]. We present a new piece of equipment, an exchange bougie (Cook (UK) Ltd). This study evaluates the exchange bougie as a means of performing tracheal intubation. The exchange bougie is 57 cm long with external and internal diameters of 6.5 mm and 4.0 mm respectively. Its side walls are sufficiently rigid so as to prevent it buckling when a tracheal tube is railroaded over it and it is supplied with a 15-mm male connector and so may be used for ventilation. The exchange bougie can be mounted on a FOL and passed into the trachea and guided to the larynx by an LMA. A tracheal tube may then be railroaded over the exchange bougie. A similar technique has been reported in a single patient [3].

Twenty-four adult patients were studied. Anaesthesia was induced with fentanyl, 1.0 $\mu g\ kg^{-1}$ and a sleep dose of propofol; neuromuscular block was produced with atracurium 0.5 $mg\ kg^{-1}$. Anaesthesia was maintained with oxygen and isoflurane. After 3 min an unmodified laryngeal mask airway was inserted, size 3 for women and size 4 for men.

A FOL with an exchange bougie mounted on it was introduced through a tracheal tube connector with a sealed side port. The

FOL was advanced until the larynx was seen. The view of larynx was graded: full, obstructed or not seen. The larynx was then entered and the exchange bougie was advanced into the trachea. The FOL and the LMA were then removed leaving the exchange bougie, over which a tracheal tube was railroaded. The exchange bougie was then removed. The tracheal tube position was then verified fibreoptically. Ease of entering the larynx and of railroading the tracheal tube were scored: easy, difficult or impossible. The period from induction of anaesthesia to completion was timed. Twelve intubations were performed by a consultant experienced in fibreoptic intubation and 12 by a registrar inexperienced in this field.

The average age was 40 yr (SD 15 yr), the average weight was 76 kg (SD 14 kg). All the patients were successfully intubated. There were no significant desaturations (i.e. $Sa_{O_2} < 95\%$).

The view of the larynx was full in 96%. Passage into the larynx and subsequent railroading of a tracheal tube were found to be easy in all patients studied. Mean time from induction of anaesthesia to completion was 357 (SD 78) s.

There was little difference between the results obtained by the experienced fibreoptic intubator compared with the inexperienced investigator, both learning the technique quickly.

The exchange bougie has not been evaluated previously. This technique may permit orotracheal intubation to be performed when direct visualization of the larynx is not possible, either electively or in an emergency. It is a simple technique that may be learnt easily and performed by the inexperienced fibreoptic intubator.

Key words

Intubation tracheal, technique. Equipment, exchange bougie.

References

1. Brimacombe J, Berry A. *Anesthesia and Analgesia* 1993; 77: 398–399.
2. Payne J. *Anaesthesia* 1989; 44: 865.
3. Logan S, Charters P. *Anaesthesia* 1994; 49: 543–544.

Effect of reduced density gas breathing on oxygenation in ventilated anaesthetized patients

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Anaesthesia produces an increase in alveolar to arterial (A-a) oxygen tension gradient in both ventilated and spontaneously breathing patients. Reducing the breathing gas density using helium in awake volunteers [1] and ventilated animals [2] caused an unexpected increase in (A-a) gradient. We have found the opposite to be the case in anaesthetized spontaneously breathing patients [3] and wished to see if this was also the case when patients were ventilated mechanically.

Ten ASA I-III patients with normal spirometry undergoing elective surgery were selected. Each patient acted as his or her own control, and was anaesthetized using propofol, alfentanil and atracurium. They were intubated and started on propofol, alfentanil and atracurium infusions. The breathing system consisted of a circle circuit with a carbon dioxide absorber and a mixing box on the expiratory limb to measure mixed expired gas. A Pneupac ventilator was connected in place of the reservoir bag. Each patient was chosen randomly to breathe either 40% oxygen in helium or 40% oxygen in nitrogen as the first gas. The fresh gas flow was set to 4 litre min^{-1} for 20 min. Gas flow was then reduced to 300 ml min^{-1} (Capnomac sampling rate 200 ml min^{-1}), the expiratory valve was closed and after a further 5 min, inspired, end-tidal and mixed expired oxygen and carbon dioxide were measured. The second gas mixture was then introduced and the procedure repeated.

There was no difference in minute ventilation or end-tidal carbon dioxide. The A-a oxygen tension gradient was calculated from the alveolar gas equation of Filley, Mackintosh and Wright. Table 10 shows that there was no difference in Pa_{O_2} and no difference in A-a oxygen tension gradient between the groups. However, in the presence of helium, both the arterial carbon dioxide and the a-A carbon dioxide tension gradient were greater than in the presence of nitrogen.

The A-a oxygen tension gradient is not changed by helium, which is not the case when patients are breathing spontaneously [3]. The a-A D_{CO_2} was again higher with helium.

It is postulated that in ventilated patients, reducing breathing gas density limits ventilation distribution or the importance of the effect of diffusion on gas exchange is reduced.

Table 10 Mean partial pressures (SD) in the two groups (kPa)

	Pa_{O_2}	Pa_{CO_2}	$D(A-a)_{O_2}$	$D(a-A)_{CO_2}$
He/O_2	18.03 (5.07)	5.26 (0.67)	17.81 (4.31)	1.69 (0.42)
N_2/O_2	17.39 (6.05)	4.85 (0.58)	16.61 (5.81)	1.17 (0.44)
P	NS	< 0.001	NS	< 0.001

Key words

Gases non-anaesthetic, helium. Oxygen, gradients.

Acknowledgement

We wish to thank BOC Healthcare for their support.

References

1. Liese W, Muysers K, Pichotka JP. *Pflügers Archives* 1970; 321: 316–331.
2. Christopherson SK, Hlastala MP. *Journal of Applied Physiology* 1982; 52: 221–5.
3. Devine A, Beatty PCW, Mortimer AJ, Campbell IT. *British Journal of Anaesthesia* 1995; 75(5): 653P–654P.

POSTER PRESENTATIONS

Computer-controlled infusion of propofol for long neurosurgical procedures

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Computer-controlled infusion of propofol for operations of intermediate duration is well documented. This study investigated the performance of such a system during long neurosurgical procedures.

Fifteen patients aged 23–52 yr gave written informed consent for inclusion in the study. Anaesthesia was induced and maintained with a computer-controlled infusion of propofol using variables reported for adult patients [1]. The target concentration was titrated according to clinical requirement. Arterial blood samples were taken at 30–60-min intervals during the infusion, and at 0, 1, 2, 4, 6, 8, 10, 15 and 20 min after stopping the infusion. Propofol concentration was measured using high performance liquid chromatography. The performance of the system was assessed using the median performance error (MDPE), median absolute performance error (MDAPE), wobble and divergence [2] (table 11). Individual concentration–time profiles during recovery were modelled to fit a biexponential equation using the non-linear regression program MKMODEL (Biosoft, Cambridge).

The mean duration of infusion was 7.7 (range 3.7–13.2) h. A total of 284 blood samples were taken for propofol assay. The half-time derived from modelling was shorter than that estimated using the infusion variables in 10 out of 13 patients.

Table 11 Performance measures (25th to 75th percentile)

	During infusion ($n = 15$)	Recovery ($n = 13$)
MDPE (%)	−6.5	−38.7
	(−23–10)	(−52–−24)
MDAPE (%)	19.1	39.0
	(9–31)	(25–52)
Wobble (%)	8.6	5.4
	(2–19)	(2–10)
Divergence (%/h)	0.8	7.7

Propofol pharmacokinetics remain stable during anaesthesia for neurosurgical procedures lasting up to 12 h. However, propofol concentrations during recovery were not predicted accurately.

Key words
Anaesthetic techniques, i.v. Drug delivery, computerized. Anaesthetics i.v., propofol.

References

1. Marsh B, White M, Morton N, Kenny GNC. *British Journal of Anaesthesia* 1991; **67**: 41–48.
2. Varvel JR, Donoho DL, Shafer SL. *Journal of Pharmacokinetics and Biopharmaceutics* 1992; **20**: 63–94.

Is the neuronal dihydropyridine binding site on L-type calcium channels a target for local anaesthetic agents?

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As part of a broader programme of research we have recently shown that i.v. anaesthetics interact with neuronal L-type voltage sensitive calcium channels (VSCCs) [1]. Sugiyama and Muteki suggest that local anaesthetics may also interact with L-type VSCCs [2]. In this study we have examined the interaction of procaine, prilocaine, lignocaine, bupivacaine and tetracaine with the 1,4-dihydropyridine (DHP) binding site in rat cerebrocortical membranes.

Rat cortical membranes were prepared in Tris.HCl 50 mmol litre^{-1}, pH 7.4 by homogenization and centrifugation. Binding assays were performed in 1 ml volumes of Tris.HCl 50 mmol litre^{-1}, pH 7.4 for 90 min at room temperature using approximately 200 µg of protein. Non-specific binding was defined in the presence of nifedipine 10^{-5} mol litre^{-1} and bound and free radioactivity were separated by vacuum filtration. The effects of local anaesthetics were determined by displacement of [^{3}H]PN200-110 0.2 nmol litre^{-1}. The concentration of displacer producing 50% displacement was corrected for the competing mass of [^{3}H]PN200-110 using a K_d 59 pM [1] to yield K_{50}.

All local anaesthetics tested displaced [^{3}H]PN200-110 dose-dependently with K_{50} values shown in table 12. There was a significant correlation ($r^2 = 0.895$, $P = 0.015$) between log K_{50} and the log octanol:buffer partition coefficient [3].

These data suggest that, in addition to the classic sodium channel block, local anaesthetic agents also interact with L-type VSCCs. Further studies will examine the role of the phenylalkylamine and benzothiazepine binding site on these channels.

Key words
Calcium channel block. Anaesthetics local. Dihydropyridines.

References

1. Hirota K, Lambert DG. *British Journal of Anaesthesia* 1996; **76**: 591P.
2. Sugiyama, K, Muteki T. *Anesthesiology* 1994; **80**: 1369–1378.
3. Strichartz GR, Sanchez V, Arthur GR, Chafetz R, Martin D. *Anesthesia and Analgesia* 1990; **71**: 158–170.

Table 12 Effects of local anaesthetics on [^{3}H]PN200-110 binding (mean (SEM) $n = 6$ each.) *Determined at 25 °C

Agent	K_{50}(mmol litre^{-1})	Log K_{50}(mol litre^{-1})	$\text{Log}_{(\text{octanol:buffer})}$*
Procaine	2.23±0.22	−2.65	1.91
Prilocaine	2.06±0.11	−2.69	2.11
Lignocaine	1.24±0.30	−2.91	2.48
Tetracaine	0.75±0.12	−3.12	3.56
Bupivacaine	0.48±0.05	−3.32	3.41

Assessment of vocal cord function using tussometry

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Tussometry is a technique for assessing laryngeal function by measuring cough peak flow rate (CPFR) and the time taken to achieve this, the peak velocity time (PVT) [1]. It has been used to assess vocal cord function postoperatively [2]. However, it has been shown that PVT is directly related to CPFR, which in turn bears a direct relation to lung volume during a cough manoeuvre [3]. It has been suggested that interpretation of tussometry is effort independent and our aim was to investigate this.

We studied the expired airflow waveform of 11 healthy volunteers (9 males), mean age 32 (range 22–54) yr. After familiarization with the technique, each subject gave a maximum cough at three different lung volumes; at total lung capacity (TLC), at the end of normal inspiration (VT) and at the end of normal expiration (FRC), and a cough with submaximal effort at TLC.

We found that CPFR and PVT are dependent upon both lung volume and cough effort (table 13). Effect of volume: PVT, $P < 0.05$; CPFR, $P < 0.02$ (Friedman). Effect of effort: PVT, $P < 0.05$; CPFR, $P < 0.05$ (Wilcoxon).

Our results coincide with previous findings that PVT varies directly with CPFR at varying lung volumes [3]. However, there is an increase in PVT and a decrease in CPFR with a reduction in cough effort. In two volunteers, CPFR was greater when submaximal effort was applied.

Key words
Cough. Measurement techniques, tussometry.

References

1. Murty GE, Lancaster P, Kelly PJ. *Clinical Otolarynology* 1991; **16**: 248–251.
2. Lamb JM, Murty GE, Slater RM, Aitkenhead AR. *British Journal of Anaesthesia* 1993; **70**: 478P.
3. Mahajan RP, Singh P, Murty GE, Aitkenhead AR. *British Journal of Anaesthesia* 1994; **72**: 298–301.

Perioperative pharmacokinetics of transdermal fentanyl in young and elderly patients

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Transdermal fentanyl is indicated for the treatment of pain in patients with malignancy. Although it is not recommended for postoperative pain, these patients may present for surgery and it may be appropriate to continue its use in the perioperative period. Perioperative transdermal fentanyl pharmacokinetics have been described [1] but there are few data comparing young and elderly patients.

Two groups of patients (elderly mean (range) 73.7 (64–82) yr; young 32.7 (25–38) yr) scheduled for lower abdominal surgery

Table 13 Effect of different lung volumes and cough effort on peak velocity time (PVT) and cough peak flow rate (CPFR) (median (range))

	Total lung capacity	End of normal inspiration (VT)	End of normal expiration (FRC)	Submaximal effort (TLC)
CPFR (litre min^{-1})	590 (450–750)	309 (130–570)	275 (150–360)	543 (310–710)
PVT (ms)	38 (13–61)	28 (5–36)	21 (13–31)	52 (32–85)

Table 14 Mean (SD) pharmacokinetic values. No significant differences except pseudo T_{max} (time at the start of the apparent plateau). $**P = 0.01$, Mann–Whitney *U* test. C_{ss} = mean concentration during plateau. ¶ = time after patch removal

	Young	Elderly
T_{max} (h)	24.5 (10.3)	28.1 (12.9)
pseudo T_{max} (h)	9.2 (6.5)	16.3 (6.1)**
C_{max} (ng ml^{-1})	2.0 (0.8)	1.3 (0.7)
C_{ss} (ng ml^{-1})	1.4 (0.6)	1.1 (0.6)
$AUC_{0-\infty}$ (ng h^{-1} ml^{-1})	115 (52)	113 (55)
¶C_{10h} (ng ml^{-1})	0.6 (0.4)	0.7 (0.4)
¶C_{30h} (ng ml^{-1})	0.4 (0.3)	0.5 (0.4)

were studied (20 total). Exclusion criteria were weight < 50 or > 100 kg and significant CNS, respiratory, cardiac, hepatic or renal disease. A fentanyl patch (50 μg h^{-1}, Janssen-Cilag) was applied to the upper anterior chest and temazepam 20 mg given orally 2 h before surgery. Anaesthesia was induced with a sleep dose of thiopentone and maintained with enflurane and nitrous oxide in 33% oxygen. Tracheal intubation was facilitated with atracurium and the lungs ventilated to normocapnia. I.v. morphine 0.2 mg kg^{-1} (young) or 0.1 mg kg^{-1} (elderly) was given. Neuromuscular block was reversed with neostigmine 2.5 mg and atropine 1.2 mg.

Morphine was available via PCA (bolus 1 mg, lock-out time 5 min) during the study. Vital signs and pain scores were recorded regularly and arterial haemoglobin oxygen saturation was measured continuously. The patch was removed 72 h after application.

Blood samples (5 ml) were taken from a venous cannula at 0, 2, 4, 8, 12, 20, 24, 30, 48, 54 and 72 h after patch application and at 0.5, 1, 2, 4, 6, 10, 20, 24 and 30 h after removal. Plasma was separated and stored at −20 °C before measurement of fentanyl concentration by radioimmunoassay (lower limit of detection 2 pg ml^{-1}) [2].

One elderly patient received fentanyl at induction (data not analysed). Patches were removed before the end of the study in three elderly (two respiratory depressions, one postoperative haemorrhage) and two young patients (one nausea, one dislike of blood sampling).

There were no significant differences in standard pharmacokinetic values (table 14). However, in common with many pharmacokinetic studies, the power of these data are low. Significant differences in pseudo T_{max} may reflect reduced skin perfusion in the elderly. The incidence of respiratory depression confirms the view that transdermal fentanyl is not appropriate for postoperative pain management in opioid-naive patients.

Key words
Analgesics opioids, fentanyl. Drug delivery, transdermal. Pharmacokinetics.

Acknowledgement

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References

1. Duthie DJR, Rowbotham DJ, Wyld R, Henderson PD, Nimmo WS. *British Journal of Anaesthesia* 1988; **60**: 614–618.
2. Bower S, Hull CJ. *British Journal of Anaesthesia* 1982; **54**: 871–977.

Interaction of vecuronium with recombinant human m2 muscarinic receptors

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We have recently shown that a range of steroidal neuromuscular blocking agents, including vecuronium, interact with the m2 muscarinic receptors present in the rat heart [1]. The interaction of vecuronium was complex yielding two affinity values. However, the major proportion of the binding (80%) occurred with relatively high affinity (K_i 216 nmol $litre^{-1}$). A major criticism of this study relates to the possibility of species differences in the potencies of neuromuscular blocking agents. We have therefore re-evaluated the interaction of vecuronium with recombinant human m2 muscarinic receptors expressed in Chinese hamster ovary (CHOm2) cells.

CHOm2 cells maintained in minimum essential medium at 37 °C in 5% carbon dioxide in air were passaged weekly and refed twice weekly. Muscarinic receptor binding studies were performed in 1 ml volumes of HEPES 20 mmol $litre^{-1}/Mg^{2+}$ 1 mmol $litre^{-1}$ (pH 7.4) buffer containing approximately 150 μg of membranes. In saturation experiments to calculate receptor density (B_{max}) and equilibrium dissociation constant (K_d) cells were incubated with increasing concentrations (0.007–0.867 nmol litre) of a radiolabelled muscarinic antagonist *n*-methyl-scopolamine ([^{3}H]NMS). the affinity of vecuronium and methoctramine (as an m2 selective reference compound) was estimated by displacement of a fixed concentration of NMS (~ 0.4 nmol $litre^{-1}$) with increasing concentrations of vecuronium (10^{-5}–3^{-10} mmol $litre^{-1}$). Tissue was incubated for 1 h at 37 °C and non-specific binding was assessed in the presence of atropine 10 μmol $litre^{-1}$. Bound and free radioactivity were separated by rapid vacuum filtration onto Whatman GF/B filters. B_{max} and K_d were calculated according to Scatchard [2]. The concentration of vecuronium and methoctramine producing 50% displacement of specific binding was corrected for the competing mass of NMS according to Cheng and Prusoff [3] to yield the affinity constant K_i.

The binding of [^{3}H]NMS was dose-dependent and saturable with a B_{max} and K_d of 165 (13) fmol mg^{-1} protein and 0.15 (0.01 nmol $litre^{-1}$ ($n = 5$) respectively. The binding of [^{3}H]NMS was displaced dose-dependently by methoctramine with a K_i of 2.34 (0.17) nmol $litre^{-1}$ ($n = 5$) confirming the expression of a homogeneous population of m2 muscarinic receptors. Vecuronium also produced a dose-dependent displacement of [^{3}H]NMS binding with a K_i of 127 (24) nmol $litre^{-1}$ ($n = 6$).

These data, in cells expressing the recombinant human m2 muscarinic receptor, confirm our previous findings with the rat m2 muscarinic receptor that there is a potent interaction of vecuronium with m2 muscarinic receptors. The K_i value in human appeared approximately twofold more potent than that seen in the rat. Further mechanistic studies are currently under way.

Key words
Neuromuscular block, Vecuronium. Receptors, human muscarinic. Model, cell culture.

Acknowledgements

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References

1. Appadu BL, Lambert DG. *British Journal of Anaesthesia* 1994; **72**: 86–88.

2. Scatchard G. *Annals New York Academy of Sciences, USA* 1949; **52**: 660–672.
3. Cheng YC, Prusoff WM. *Biochemistry and Pharmacology* 1973;; **22**: 3099–3108.

Measurement of desflurane partial pressure in blood

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The measurement of the partial pressure of volatile anaesthetics in blood conventionally requires repeated equilibrations of blood with air in the headspace of the vessel containing it [1]. We have previously used head space analysis successfully to measure the partial pressure of isoflurane in blood but met difficulties measuring desflurane with the same technique. We describe a simple modification of the standard method.

In our standard method a 2-ml blood sample is placed in a 5-ml vial and agitated in a waterbath at 37 °C for 15 min, the isoflurane concentration in the vial headspace measured using a gas chromatograph (GC), then the headspace flushed with room air. This equilibration-measurement-flush cycle is repeated three times. A least-squares fit of the four headspace concentrations to an exponential washout allows calculation of both the initial partial pressure and the blood-gas solubility coefficient.

We evaluated this technique using blood in a IL-237 tonometer with 3% desflurane in air as the equilibrating gas. We found a systematic underestimate of the initial partial pressure and an overestimate of the blood gas solubility of desflurane compared with published data. We blamed this on incomplete flushing of the headspace between equilibrations because of trapping of desflurane in bubbles and froth within the vial. The effect of this will be much greater with desflurane than with isoflurane because desflurane is less soluble in blood. We have therefore modified the technique.

After the first equilibration and desflurane measurement, the vial was opened, blood drawn into a syringe from the bottom of the sample and 1 ml was transferred into a new 5 ml vial. For simplicity, only one more headspace equilibration and measurement was made. Let P_0 be the partial pressure of desflurane in the sample when it was first drawn; let P_1 and P_2 be the partial pressures after the first and second equilibrations respectively; let V_v, V_1 and V_2 be the volumes of the vial (4.8 ml), the first blood sample (2 ml) and the sample transferred (1 ml) respectively; let λ be the blood gas coefficient; and let T_{lab} be the laboratory air temperature in K. The GC readings are multiplied by the factor $1.03 \times 210/T_{lab}$ to correct for pressure changes in the vial as a result of humidification and warming of the air. Then equating the amount of desflurane in the vial before and after each equilibration:

$$P_0 V_1 \lambda = P_1 V_1 \lambda + P_1(V_v - V_1)$$

and

$$P_1 V_2 \lambda = P_2 V_2 \lambda + P_2(V_v - V_2)$$

The second equation is solved for λ and this value is used to determine P_0 in the first. P_0 is corrected to dry gas to match the tonometer gas sample. The mean error in the sample measurement ($n = 21$) was −0.2% of the tonometer reading, and the 95% CI for an individual measurement was ±8%. Although the variation in our results is greater than in published work using isoflurane, comparable results for desflurane are not available.

Key words

Anaesthetics volatile, desflurane. Measurement techniques, gas exchange.

Reference

1. Knill RL, Lok PYK, Strupat JP, Lam AM. *Canadian Anaesthetists' Society Journal* 1983; **30**: 155–161.

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CORRESPONDENCE

CSF progesterone and spread of subarachnoid anaesthesia in pregnancy

Sir,—Hirabayashi and colleagues [1] suggested that a sustained (at least 3–4 months) increase in cerebrospinal fluid (CSF) progesterone concentration may be necessary to produce enhanced spread of spinal anaesthesia in pregnant women. We believe that these conclusions are misleading and unsupported by the results.

Maximum cephalad spread of analgesia was quoted as being higher in the second trimester compared with the first, but there were no results of statistical tests that directly compared these two trimesters. Median maximum cephalad spread of analgesia was the same (T4) in the first and second trimesters, and this makes it unlikely, although not impossible, that there was a significant difference between the two groups. The figures do not show all data points, perhaps because overlapping points are not separated, and it was impossible for us to confirm the results.

The CSF progesterone concentration data were also surprising. CSF progesterone concentrations were said to be increased similarly in the early and middle stages of pregnancy. This appeared to form the basis for Hirabayashi and colleagues suggesting that chronic exposure to progesterone increased spread of spinal anaesthesia (assuming that there really is increased spread in the second trimeter compared with the first). However, the results stated that there was ***no significant*** increase in CSF progesterone concentration during early and middle pregnancy compared with the control group. The CSF progesterone concentration data were further complicated by the larger number of patients with undetectable progesterone, even at term gestation. Other studies have detected CSF progesterone concentrations in all patients [2, 3], with mean concentrations at term gestation approximately double those reported by Hirabayashi and colleagues.

Given the wide variation in both the CSF progesterone concentration and the spread of spinal anaesthesia, we are not convinced that a meaningful association can be made between chronic exposure to progesterone and increased spread of analgesia. The study design certainly does not permit one to conclude that progesterone may be a causative factor.

The suggestion that chronic exposure to progesterone may be necessary for increased sensitivity of nerves to local anaesthetics was derived from a series of *in vitro* studies using rabbit vagus nerves [4]. However, the same research group has recently reported that bupivacaine conduction block of B and C fibres in desheathed vagus nerves was similar in pregnant and non-pregnant rabbits [5]. It was concluded that previous data on progesterone and nerve sensitivity to local anaesthetics were a result of increased diffusion of bupivacaine through the nerve sheath rather than a direct action on the nerve itself. Therefore, the effect of progesterone on nerve block after intrathecal administration of local anaesthetics remains uncertain.

Hirabayashi and colleagues quickly dismissed mechanical factors as a possible cause for increased spread of spinal anaesthesia in the second trimester, but did not provide supporting evidence. Anatomically, the gravid uterus is first palpable above the pubic symphysis at 12 weeks' gestation. By 16 weeks' gestation, the uterus extends above the sacral promontory where the inferior vena cava usually bifurcates [6]. Caval compression may occur in early pregnancy. When pregnant women of 13–16 weeks' gestation were placed supine, direct femoral venous pressure measurements increased by 50% [7]. It is thus possible that a progressive increase in caval compression throughout pregnancy may contribute to a progressive increase in the spread of spinal anaesthesia.

Although not specifically stated in the article, we wonder if data from some of the patients in this study have been reported previously [8]. In that article, it was also concluded that maximum cephalad spread of analgesia was higher in the second trimester compared with the first. Again, there were no statistics provided that directly compared the two trimesters.

By arguing that spread of sensory block in the second trimester is greater than that in the first trimester but similar to that at term, the authors have implied in both reports that there is a cut-off point in the second trimester where spread of sensory block increases. Given the progressive nature of pregnancy and artificial division of gestation into trimesters, it may be just as likely that there is a gradual increase in spread of sensory block from the non-pregnant state to term gestation, whatever the cause(s).

We also suggest that there may be bias in the conclusion that CSF progesterone concentrations were greater in twin pregnancies compared with singleton pregnancies in the third trimester. Figure 1 shows that in the third trimester group (25–36 weeks), at least four of the singleton pregnancies were between 25 and 27 weeks, while none of the twin pregnancies was less than 32 weeks. There is an inconsistency between table 1, which lists the smallest weight in the second trimester group as 50 kg, and table 2, where the corresponding minimum weight is 40 kg.

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1. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Cerebrospinal fluid progesterone in a pregnant women. *British Journal of Anaesthesia* 1995; 75: 683–687.
2. Datta S, Hurley RJ, Naulty S, Stern P, Lambert DH, Concepcion M, Tulchinsky D, Weiss JB, Ostheimer GW. Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women. *Anesthesia and Analgesia* 1986; 65: 950–954.
3. Gershon RY, Zikowski DM, Johansen J. CSF and plasma progesterone concentrations in the parturient. *Anesthesiology* 1994; 81: A1156.
4. Bader AM, Datta S, Moller RA, Covino BG. Acute progesterone treatment has no effect on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesthesia and Analgesia* 1990; 71: 545–548.
5. Lambert DH, Flanagan HL, Fenton T, Datta S. The effect of desheathing on conduction blockade by bupivacaine in nerves isolated from pregnant and nonpregnant rabbits. *Anesthesia and Analgesia* 1994; 78: S232.
6. Kochenour NK. Normal pregnancy and prenatal care. In: Scott JR, Disaia PJ, Hammond CB, Spellacy WN, eds. *Danforth's Obstetrics and Gynecology*. Philadelphia: JB Lippincott, 1994; 67–104.
7. McLennan CE. Antecubital and femoral venous pressure in normal and toxemic pregnancy. *American Journal of Obstetrics and Gynecology* 1943; 45: 568–591.
8. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Spread of subarachnoid hyperbaric amethocaine in pregnant women. *British Journal of Anaesthesia* 1995; 74: 384–386.

Sir,—In our study, we found a small, non-significant increase in CSF progesterone concentration in the first trimester and second trimester groups. In addition, we found higher cephalad spread of analgesia in the second trimester group compared with the non-pregnant group. Cephalad spread of analgesia in the first trimester group was similar to that of the non-pregnant group. From this we concluded that not only a minimum concentration of progesterone in CSF but also a particular duration of exposure to elevated CSF progesterone concentrations may be necessary for enhancement of spread of spinal anaesthesia. I studied the report of Lambert and colleagues [1] and understood that the effect of pregnancy on neural block observed in their earlier studies [2, 3] may be caused by increased diffusion of bupivacaine through the nerve sheath and not a direct effect on the nerve itself. Both CSF progesterone concentration and spread of spinal anaesthesia show a wide variation in clinical practice. Consequently, I also understand that further studies are needed to draw final conclusions on the direct involvement of progesterone with pregnancy-induced enhancement of spinal anaesthesia.

Because unfortunately we did not measure plasma progesterone concentration simultaneously in our study, we cannot determine the reason why there are some disparities in CSF progesterone concentration between previously reported studies and ours. I suggest that racial differences might contribute to the disparities.

By 20 weeks of pregnancy the uterus is spheroid, and thereafter becomes more and more elongated as the conceptus is converted from spheroid to cylindrical form [4]. At 16 weeks, the fundus of the uterus rises to approximately half of the distance between the symphysis and the umbilicus, and it is at the umbilicus by 20 weeks [5]. The spheroidal uterus may occupy a considerable space in the pelvic cavity and may increase femoral venous pressure. However, it remains uncertain if this increase in femoral venous pressure is accompanied by engorgement of the extradural venous plexus. Many patients with gynaecological tumours have an increased femoral venous pressure comparable in magnitude with that seen in the latter months of pregnancy [6]. However, to our knowledge, there are no studies which demonstrate that such patients usually show higher spread of spinal anaesthesia compared with patients without gynaecological tumours. I suggest that the inferior vena cava, which is formed on the right side of the 5th lumbar vertebra by the junction of the two common iliac veins [7, 8], may not be compressed by the spheroidal uterus. Nevertheless, because there are no studies which have determined when the enlarged pregnant uterus begins to compress the inferior vena cava and engorge the extradural venous plexus [9], further studies focusing on this issue should be performed.

We reported previously on the spread of subarachnoid hyperbaric amethocaine in pregnant women [10]. In that report, we collected data on the spread of sensory block from 90 patients. We anaesthetized these patients with amethocaine 8 mg, but did not collect any CSF. The patients in our previous study differed from the 134 patients in the present study in which 1 ml of CSF was withdrawn just before administration of amethocaine 8 mg. Both the methodology and patients examined in these two studies were different.

I agree with the suggestion that artificial division of pregnancy into trimesters is not possible for evaluation of pregnancy-induced enhancement of spread of spinal anaesthesia which may increase gradually. However, I believe that this division of pregnancy into trimesters, which is standard practice in prenatal care, provides useful information in clinical management of spinal anaesthesia. Pregnancy during the first trimester does not affect spread of spinal anaesthesia, while pregnancy during the second trimester until term enhances it. What is required is to determine when enhancement begins to develop, especially in the second trimester of pregnancy.

We had compared CSF progesterone concentrations in 40 twin pregnancies (median 36 (range 12–38) weeks of pregnancy) with those in 81 singleton pregnancies (37 (8–41) weeks of pregnancy), when we analysed the data in the present study. The results confirmed that CSF progesterone concentrations were greater in twin pregnancies than in singleton pregnancies (mean 1.51 (SD 1.33) ng ml^{-1} *vs* 0.73 (0.83) ng ml^{-1}; $P = 0.001$). Finally, table 1 in our article contains an error. The smallest weight in the second trimester group was 40 kg (not 50 kg). This typographic error has not affected the statistical analyses and we apologize for this mistake.

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1. Lambert DH, Flanagan HL, Fenton T, Datta S. The effect of desheathing on conduction blockade by bupivacaine in nerves isolated from pregnant and non-pregnant rabbits. *Anesthesia and Analgesia* 1994; **78**: S232.
2. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG. Differential sensitivities of mammalian nerve fibers during pregnancy. *Anesthesia and Analgesia* 1983; **62**: 1070–1072.
3. Flanagan HL, Datta S, Lambert DH, Gissen AJ, Covino BG. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesthesia and Analgesia* 1987; **66**: 123–126.
4. Bonica JJ. Maternal anatomic and physiologic alterations during pregnancy and parturition. In: Bonica JJ, McDonald JS, eds. *Principles and Practice of Obstetric Analgesia and Anesthesia*, 2nd Edn. Baltimore: Williams & Wilkins, 1995; 45–82.
5. Kochenour NK. Normal pregnancy and prenatal care. In: Scott JR, Disaia PJ, Hammond CB, Spellacy WN, eds. *Danforth's Obstetrics and Gynecology*, 7th Edn. Philadelphia: JB Lippincott, 1994; 67–104.
6. McLennan CE. Antecubital and femoral venous pressure in normal and toxemic pregnancy. *American Journal of Obstetrics and Gynecology* 1943; **45**: 568–591.
7. Woodburne RT, Burkel WE. *Essentials of Human Anatomy*, 8th Edn. New York: Oxford University Press, Inc., 1988.
8. Moore KL. *Clinically Oriented Anatomy*, 3rd Edn. Baltimore: Williams & Wilkins, 1992.
9. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft-tissue anatomy within the vertebral canal in pregnant women. *British Journal of Anaesthesia* 1996; **77**: 153–156.
10. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Spread of subarachnoid hyperbaric amethocaine in pregnant women. *British Journal of Anaesthesia* 1995; **74**: 384–386.

Sevoflurane

Sir,—I read with interest the recent review article on sevoflurane [1]. There are, however, two points that were inadequately considered.

The section on renal toxicity was largely limited to the effects of increased serum fluoride concentrations; the potential for renal toxicity caused by renal tubular damage after production of compound A was questioned [1]. The authors failed to highlight that the clinical studies to date, although without reports of nephrotoxicity, have largely examined indices of glomerular function [2, 3]. The functional reserve of the kidney prevents renal toxicity being detected, except in circumstances of severe injury. Studies that have attempted to assess tubular damage have used relatively high fresh gas flows, thereby limiting production of compound A [4]. This also reflects the difficulty in accepting the large clinical experience gained with sevoflurane in Japan, because of the commonly used high fresh gas flows. The safety of sevoflurane in low-flow anaesthesia remains to be established.

In the discussion regarding the renal toxicity of compound A, the authors mentioned a conflict of interest in a previous study [5] and the effect this may have on objectivity [6]. The source of research funding, and the possible effect on bias and integrity, are important issues that should always be declared. In contrast, the authors failed to acknowledge their own previous involvement with Abbott Laboratories [7]. This clearly represents a similar conflict of interest to the one they highlighted. Omission of this fact from the article represents a considerable oversight that must be addressed. As Dr Saidman stated "the overriding opinion is that all relevant financial interests and potential conflicts be disclosed, which at a minimum allows the audience, be it the readership of a journal or those attending a lecture, to judge themselves whether the data being described are accurate, and that the conclusions and recommendations are fairly stated" [6].

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1. Smith I, Nathanson M, White PF. Sevoflurane—a long-awaited volatile anaesthetic. *British Journal of Anaesthesia* 1996; **76**: 435–445.
2. Bito H, Ikeda K. Closed circuit anesthesia with sevoflurane in humans. *Anesthesiology* 1994; **80**: 71–76.
3. Frink EJ, Malan TP, Morgan SE, Brown EA, Malcomson M, Brown BR. Quantification of the degradation products of sevoflurane in two CO$_2$ absorbants during low-flow anaesthesia in surgical patients. *Anesthesiology* 1992; **77**: 1064–1069.
4. Higuchi H, Sumikura H, Sumita S, Arimura S, Takamatsu F, Kanno M, Satoh T. Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. *Anesthesiology* 1995; **83**: 449–458.
5. Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL. Toxicity of compound A in rats. Effect of a 3-hour administration. *Anesthesiology* 1994; **80**: 556–565.
6. Saidman LJ. Unresolved issues relating to peer review, industry support of research and conflict of interest. *Anesthesiology* 1994; **80**: 491–492.
7. Fredman B, Nathanson MH, Smith I, Wang J, Klein K, White PF. Sevoflurane for outpatient anesthesia: A com-

parison with propofol. *Anesthesia and Analgesia* 1995; **81**: 823–828.

Sir,—Thank you for allowing us to respond to Dr Daniel. Our section on renal toxicity was primarily directed towards elevated serum fluoride concentrations because human nephrotoxicity has occurred previously with methoxyflurane. Until relatively recently, toxicity was believed to be an inevitable consequence of exceeding a "threshold" serum fluoride concentration. As concentrations in excess of 50 μmol litre^{-1} are not infrequently produced by exposure to clinically relevant concentrations of sevoflurane, it was necessary to examine the evidence for fluoride-related nephrotoxicity with sevoflurane. It was partly the lack of such toxicity which has led to an increased understanding of the relationship between fluoride-producing anaesthetics and renal damage.

In contrast, it is not known if compound A is nephrotoxic to *humans* or, if it is, by what mechanism or at what concentrations. In the rat, compound A *is* nephrotoxic. The LD_{50} is approximately 1000 ppm, although histological signs of tubular damage are seen in rats exposed to concentrations of 50 ppm or more of compound A. It is not yet clear what is the natural history of these lesions in rats. Of greater importance, it is by no means certain that compound A is as toxic to humans as it is to rats. Recent evidence from Kharasch's group [1] suggests that compound A has to undergo further metabolism to produce nephrotoxicity. The pathway by which this occurs is approximately 10 times more active in rodents compared with humans, suggesting that compound A may indeed be substantially less harmful to humans [1]. This is supported by the absence to date of *any* signs of renal dysfunction (tubular or glomerular) in humans exposed to sevoflurane under a wide range of clinical conditions. A recent Japanese study showed no evidence of renal or hepatic toxicity after 13 MAC-h of anaesthesia in 50 patients exposed to sevoflurane at a total flow rate of 1 litre min^{-1} [2]. Rather than "limiting compound A production", this regimen produced a mean level of 24.6 ppm (range 13.6–41.3 ppm). Nevertheless, postoperative indices of hepatic and renal function did not differ significantly from a control group who received a comparable isoflurane anaesthetic [2]. Although it is true that much of the Japanese *clinical* experience involves moderately high flows, the routine use of sevoflurane since the early 1990s in Japan has encompassed a far broader range of conditions and pre-existing pathologies than would ever be allowed within the constraints of a research project. Despite this, no pattern of renal damage has emerged. The author may be correct when he stated that "the functional reserve of the kidney prevents renal toxicity being detected except in circumstances of severe injury". However, the same mechanism also limits the clinical significance of any such minor toxicity [3]. Finally, the Committee on Safety of Medicines has reviewed published data on sevoflurane and data on file with Abbott (which was not available to the authors of this review) and concluded that there is no evidence to support the avoidance of sevoflurane in low-flow anaesthesia.

With regard to conflict of interest, the authors have previously (in common with many other researchers) received financial support from the pharmaceutical industry to conduct clinical studies. Two of our previous studies with sevoflurane received such support [4, 5], which was openly declared when they were published. Many of the articles by other authors which we reviewed will also have received commercial support. However, the authors are not employed (partly or wholly) by Abbott, they did not receive any financial support from Abbott in association with the production of this review article, and the article was not submitted to Abbott for review before publication. In addition, some of the authors have also previously received financial support from ICI-Zeneca (the makers of propofol), Ohmeda and Pharmacia (the manufacturers and distributors of desflurane) for studies with products which could be considered commercial "rivals" to sevoflurane. For these reasons, we did not mention our previous "involvement" with (any) pharmaceutical company. In contrast, the conflict of interest referred to in our review concerned work relating to sevoflurane by an individual who is a paid consultant to Ohmeda, the manufacturers of a rival product. The authors accept that in an ideal world, all research would be totally independent of drug company finances. However, is there not a difference between industry support of research and a regular income for advising a pharmaceutical company on marketing and promotional matters? Perhaps the readership of the *British Journal of Anaesthesia* would like to judge this issue for themselves.

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1. Kharasch E, Garton K, Hankins D, Kilty C. The role of glutathione and cysteine conjugates and renal cysteine conjugate β-lyase in compound A nephrotoxicity (abstract). *Anesthesiology* 1995; **83**: A339.
2. Bito H, Ikeda K. Renal and hepatic function in surgical patients after low-flow sevoflurane or isoflurane anesthesia. *Anesthesia and Analgesia* 1996; **82**: 173–176.
3. Eger EI II. Is there equivalence between compound A and a synthetic olefin?—In reply. *Anesthesiology* 1994; **81**: 272–273.
4. Smith I, Ding Y, White PF. Comparison of induction, maintenance and recovery characteristics of sevoflurane–N_2O and propofol–sevoflurane–N_2O with propofol–isoflurane–N_2O. *Anesthesia and Analgesia* 1992; 74: 253–259.
5. Fredman B, Nathanson MH, Smith I, Wang J, Klein K, White PF. Sevoflurane for outpatient anesthesia: A comparison with propofol. *Anesthesia and Analgesia* 1995; **81**: 823–828.

Removal of extradural catheters

Sir,—Two previous communications [1, 2] have commented upon removal of extradural catheters. My experience supports the view put forward by Morris [2]. In two cases of ankylosing spondylitis who had undergone total hip replacement the junior resident was unable to remove the extradural catheter on the fourth post-operative day; in both, the extradural catheter had been inserted in the left lateral position under general anaesthesia. The lumbar spine in both patients was partially fused and the extradural placement was technically difficult. I was also unable to remove the catheter in the flexed sitting position, but on turning the patient into the left lateral position with flexion, the catheters were removed without any problems.

In the postoperative period, extradural catheters are usually removed in the flexed sitting position because of patient comfort. I suggest that in patients with technically difficult extradural catheter placement the catheter should be removed in the same position as that used for insertion and undue force should not be applied. I further suggest that the nurses and residents should be made aware of this simple manoeuvre, and the position in which a catheter has been inserted should be written on the anaesthesia records.

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1. Boey SK, Carrie LES. Withdrawal forces during removal of lumbar extradural catheters. *British Journal of Anaesthesia* 1994; 73: 833–835.
2. Morris GN. Removal of lumbar extradural catheters. *British Journal of Anaesthesia* 1995; 74: 722.

Optimal intracuff pressures with the laryngeal mask

Sir,—We read with interest the article by Morris and Marjot demonstrating that laryngeal mask airway (LMA) cuff pressures can be reduced to 22 mm Hg without significantly affecting tidal ventilation in spontaneously breathing anaesthetized patients [1]. While agreeing that reducing intracuff pressure may minimize pharyngeal morbidity, we suggest that perioperative cuff deflation to such low pressures may be potentially hazardous.

A major function of the LMA cuff during spontaneous breathing is to protect the larynx from oropharyngeal saliva. To perform this function an oropharyngeal leak pressure of up to 10 cm H_2O may be required (the approximate pressure of fluid at the posterior pharyngeal wall if the oral cavity is flooded). An intracuff pressure of 22 mm Hg may or may not be sufficient to ensure an adequate seal to prevent contamination of the larynx with oropharyngeal secretions depending on the factors outlined above. We would therefore suggest that in patients undergoing spontaneous ventilation a leak pressure of greater than 10 cm H_2O is a more useful guide to airway safety than intracuff pressure alone. Other factors, such as avoidance of lignocaine gel for lubrication, choice of correct size of LMA and ensuring that tension in the pilot balloon does not increase during nitrous oxide anaesthesia may help minimize the risks of pharyngeal morbidity.

The authors infer that pharyngeal mucosal blood flow may be significantly impaired at commonly used cuff pressures. This concept was based on a study by Marjot where mucosal pressures were calculated, but not measured directly [2]. Hamakawa, Nakamura and Kawasaki directly measured the pressure on the middle part of the outside of the LMA and showed that extracuff pressure is approximately 25 mm Hg and does not increase during oxygen–nitrous oxide anaesthesia, despite increases in intracuff pressure [3]. Although there are obvious limitations to measuring pressure at one arbitrary point, this study may help to explain why pharyngeal morbidity is uncommon. It also confirms that the relationship between intracuff and pharyngeal mucosal pressure is non-linear making guidelines based on intracuff pressures alone less useful.

It is important to distinguish between pressure in the cuff, pressure exerted by the cuff on the mucosa and pressure in the airway at which leaks occur. Unfortunately because of the nature of the anatomy surrounding the mask and the low probability that the mask is exactly the right size for any given patient, there can be no fixed relationship between these three variables. It is therefore logical to determine an intracuff pressure which provides an effective seal empirically, a "just seal" pressure. This value is higher if the mask is small relative to the anatomical space available and lower if the mask is large relative to the available space. For this reason it is sensible to choose as large a size of mask as possible in order to ensure the "just seal" pressure is as low as possible. The smaller the mark relative to the patient, the weaker the relationship between intracuff pressure and average pressure on the mucosa, as the elastic material of the cuff is being stretched relatively more than the tissues surrounding it. On the other hand, because the cuff surface becomes more rigid with increasing intracuff pressure, local high pressure points may develop if excessive stretching of a small mask is resorted to as a means of achieving a seal in a large patient. The inventor suggests that to determine correct mask size a good rule of thumb is to use the largest size which is not displaced out of the pharynx after insertion when the cuff is inflated to a pressure of 60 cm H_2O.

Finally, a new recommendation is to appear in the forthcoming updated LMA instruction manual stating that smoothest recovery is likely to be obtained by reducing intracuff pressure to the minimum required to maintain an effective seal. This must be done with care to avoid accidental laryngeal contamination and should be carried out by the anaesthetist rather than delegated to the recovery staff. Cuff overinflation may cause premature rejection of the LMA or provocation of incomplete and therefore ineffective reflex responses. This may promote laryngeal spasm or regurgitation. Full deflation of the cuff should only occur synchronously with removal of the LMA to avoid secretions entering the larynx and provoking laryngeal spasm. Alternatively, the LMA may be removed with the cuff still moderately inflated to aid more complete removal of salivary secretions.

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1. Morris GN, Marjot R. Laryngeal mask airway performance: effect of cuff deflation during anaesthesia. *British Journal of Anaesthesia* 1996; 76: 456–458.
2. Marjot R. Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa. *British Journal of Anaesthesia* 1993; 70: 25–29.
3. Hamakawa T, Nakamura S, Kawasaki Y. Intracuff pressure of the LM and pressure on the pharynx. *Journal of Clinical Anaesthesia* (*Rinsho-Masui*) 1993; 17: 1165–1167.

Sir,—Thank you for the opportunity to reply to Drs Brimacombe, Berry and Brain.

The excessively high intracuff pressures of the laryngeal mask *in situ* have been reported by various independent workers [1–3]. There are two crucial questions raised by this finding.

First, is a significant proportion of this pressure arising as a result of pressure on the adjacent pharyngeal mucosa? There is evidence to suggest that this is the case [2, 3], although no one as yet has implanted a pressure transducer into the pharyngeal mucosa. We were unable to trace the referenced work by Hamakawa, Nakamura and Kawasaki from the citation given. Our study was designed to determine if the manoeuvre of reducing intracuff volume and pressure during anaesthesia, which have been advocated by these authors and others [1, 4–6], was feasible in practice. To this end, we reduced intracuff pressure to the unequivocally "safe" pressure of 22 mm Hg (that of an estimated mucosal capillary perfusion pressure), and studied its effect on the primary function of the LMA, namely the unobstructed conveyancing of tidal ventilation from the anaesthetic breathing system to the patient's lungs. Any secondary function of laryngeal protection from oropharyngeal secretions was not investigated (although there was no evidence of this manifesting as laryngospasm, coughing, etc). We agree that unless intracuff pressure is reduced to a safe level, then monitoring is meaningless, as it is impossible to distinguish that proportion resulting from pressure on the mucosa and that of stretching the cuff. Yet, intracuff pressure monitoring is still recommended by the manufacturers and others [1, 7, 8]. The advice to deflate the cuff to a 10 cm H_2O "leak pressure" and the feeling of the "tension of the pilot balloon" would seem to be crude and unsubstantiated gauges of intracuff and therefore mucosal pressures. However, these may be the simplest methods of ensuring cuff volumes are kept to a minimum in practice.

The second question is whether pressure on the pharyngeal mucosa by the LMA cuff causes problems. Are we looking for a cure to a problem that does not exist? The LMA has rightly been embraced into anaesthetic practice throughout the world. The paucity in the international literature of morbidity resulting from the LMA cuff would indicate that the risks are very small. Perhaps it is now time to acknowledge this and dispense with the recommendation of intracuff monitoring, then the LMA could rest (or wedge) in peace.

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1. Lumb AB, Wrigley MW. The effect of nitrous oxide on the laryngeal mask cuff pressure: *in vitro* and *in vivo* studies. *Anaesthesia* 1992; 47: 320–323.
2. Marjot R. Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa. *British Journal of Anaesthesia* 1993; 70: 25–29.
3. O'Kelly SW, Heath KJ, Lawes EG. A study of laryngeal mask inflation: pressures exerted on the pharynx. *Anaesthesia* 1993; 48: 1075–1078.
4. Brimacombe J, Berry A. Laryngeal mask cuff pressures. *Anaesthesia* 1994; 49: 447–448.
5. Nagai K, Sakuramoto C, Goto F. Unilateral hypoglossal nerve paralysis following the use of the laryngeal mask airway. *Anaesthesia* 1994; 49: 603–604.
6. Brain AIJ. Course of the hypoglossal nerve in relation to the laryngeal mask airway. *Anaesthesia* 1995; 50: 82–83.
7. Brain AIJ. *The Intavent Laryngeal Mask; Instruction Manual*, 2nd Edn. Windsor: Colgate Medical Limited, 1991.
8. Asai T, Morris S. Inflation of the cuff of the laryngeal mask. *Anaesthesia* 1994; 49: 1098–1099.

Prevention of cardiovascular response to tracheal intubation

Sir,—We were interested to read the recently published article on the effects of nicardipine, diltiazem and verapamil in controlling the cardiovascular responses to tracheal intubation by Mikawa and colleagues [1]. We would like to offer some comments.

The authors stated that anaesthesia was induced in a rapid-sequence manner by administering thiopentone and vecuronium, and ventilating the lungs with 1% isoflurane and 50% nitrous oxide in oxygen, and laryngoscopy was carried out 2 min after administration of thiopentone–vecuronium. This is not the correct use of an accepted terminology. The accepted meaning of rapid-sequence induction of anaesthesia is a sequence which allows rapid intubation of the trachea without manual ventilation of the lungs and with cricoid pressure applied to prevent passive regurgitation and aspiration of gastric contents.

Verapamil is effective in attenuating the pressor response but does not control the tachycardia after laryngoscopy and intubation [2, 3]. In this study, heart rate was increased from a mean of 80 to 100 beat min^{-1} or more after administration of verapamil before laryngoscopy and intubation. With these values, it is difficult to conclude, as they did, that verapamil successfully attenuated the increase in heart rate after intubation. In their previous study using a similar anaesthetic technique, they could not demonstrate the role of verapamil in preventing the tachycardic response [2]. In this study, it may have been possible to demonstrate attenuation of tachycardia if they had omitted atropine as premedication.

With regard to measurements of plasma concentrations of adrenaline and noradrenaline, it has been shown that N-type calcium channels are responsible for release of neurotransmitters, and so-called classic calcium channel antagonists such as nicardipine, verapamil, diltiazem and others do not have much interaction with these channels [4]. On theoretical grounds it would be expected that these calcium channel blockers would have no effect on plasma concentrations of catecholamines after laryngoscopy and intubation.

Among the different methods used for attenuating undesirable cardiovascular responses to tracheal intubation, short-acting opioids appear to have a reliable and constant effect but they may contribute to postoperative respiratory depression. Lignocaine is the drug used most often, but its efficacy has been questioned in recent studies [5, 6]. Nebulized bupivacaine is only partially effective in blunting the haemodynamic response to tracheal intubation [7]. Beta blockers prevent tachycardia more than the pressor response [8] and because of their depressant effect on the myocardium, their role still remains to be defined, especially in patients with cardiac disease. A combination of esmolol and alfentanil has been shown to reliably suppress the response to laryngoscopy and intubation [9]. Clonidine and calcium channel blockers seem to be less effective in preventing haemodynamic alterations [10]. The risk of hypotension from calcium channel blockers such as nicardipine and verapamil when used with inhalation agents for maintenance of anaesthesia should be constantly borne in mind. Therefore, in clinical practice it is more appropriate to use a sufficient dose of an ultra-short-acting drug with a rapid onset to attenuate both hypertension and tachycardia. This should neither potentiate the depressant effect of anaesthetic agents used for maintenance of anaesthesia nor potentiate neuromuscular block.

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1. Mikawa K, Nishina K, Maekawa N, Obara H. Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation. *British Journal of Anaesthesia* 1996; **76**: 221–226.
2. Yaku H, Mikawa K, Maekawa N, Obara H. Effect of verapamil on the cardiovascular responses to tracheal intubation. *British Journal of Anaesthesia* 1992; **68**: 85–89.
3. Wig J, Sharma M, Baichoo N, Agarwal A. Nicardipine and verapamil attenuate the pressor response to laryngoscopy and intubation. *Canadian Journal of Anaesthesia* 1994; **41**: 1185–1188.
4. Hirota K, Lambert DG. Voltage sensitive calcium channels and anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 344–346.
5. Kobayashi TL, Watanabe K, Ito T. Lack of effect of i.v. lidocaine on cardiovascular responses to laryngoscopy and intubation. *Masui—Japanese Journal of Anaesthesiology* 1995; **44**: 579–582.
6. Singh H, Vichitvejpaisal P, Gaines GY, White PF. Comparative effects of lidocaine, esmolol, and nitroglycerin in modifying the hemodynamic response to laryngoscopy and intubation. *Journal of Clinical Anesthesia* 1995; **7**: 5–8.
7. Victory RA, Gajrai NM, Pace NA, Ostman LP, White PF. Nebulized bupivacaine attenuates the heart rate response following tracheal intubation. *Journal of Clinical Anesthesia* 1995; **7**: 9–13.
8. Vucevic M, Purdy GM, Ellis FR. Esmolol hydrochloride for management of the cardiovascular stress response to laryngoscopy and tracheal intubation. *British Journal of Anaesthesia* 1992; **68**: 529–530.
9. Korpinen R, Saarnivaara L, Siren K, Sarna S. Modification of the haemodynamic responses to induction of anaesthesia and tracheal intubation with alfentanil, esmolol and their combination. *Canadian Journal of Anaesthesia* 1995; **42**: 298–304.
10. Carabine UA, Allen RW, Moore J. Partial attenuation of the pressor response to endotracheal intubation. A comparison of the effects of intravenous clonidine and fentanyl. *European Journal of Anaesthesiology* 1992; **9**: 325–329.

Tea-total

Sir,—Is the *British Journal of Anaesthesia* introducing a neologism or is the spelling of teetotal (tea-total [1]) different east of the Pennines? Dick Turner is stirring uneasily beneath his Preston (Lancashire) tombstone which bears the inscription: "Beneath this stone are deposited the remains of Richard Turner, author of the word *Teetotal* as applied to abstinence from all intoxicating liquors, who departed this life on the 27th day of October, 1846, aged 56 years" [2].

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1. Snook NJ, O'Beirne HA, Enright S, Young Y, Bellamy MC. Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness. *British Journal of Anaesthesia* 1996; **76**: 740–743.
2. *Brewer's Dictionary of Phrase and Fable*. Great Britain: William Clowes, 1953.

Analgesia: dose-effect or pre-emptive effect?

Sir,—We were interested to read the recently published double-blind study on the influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements by Mansfield, James and Kinsella [1] and would like to offer some comments.

In this study patients undergoing abdominal hysterectomy were allocated randomly to receive one of three different analgesic regimens: morphine 0.3 mg kg^{-1} before the start of surgery (pre-high), morphine 0.15 mg kg^{-1} before surgery (pre-low) and morphine 0.15 mg kg^{-1} at the start of abdominal closure (post-low). The dose of i.v. morphine given in the recovery room, total 24-h morphine PCAS requirements and total dose of morphine in the perioperative period, including that given in theatre, were recorded. Statistical analysis revealed reduced 24 h use of morphine in the pre-high group compared with the pre-low and post-low groups. When total perioperative morphine consumption was analysed, there was a significant difference between the pre-high and post-low groups only. On the basis of these analyses the study reported evidence of pre-emptive analgesia.

We are concerned that patients given morphine 0.15 mg kg^{-1} on abdominal closure apparently received no intraoperative analgesic supplements other than 66% nitrous oxide. Could the authors comment as to how adequate analgesia was ensured in the peroperative period in order to satisfy ethical considerations in the post-low-dose group?

Is it possible the results of this study indicated that a large dose of morphine provided better analgesia than a small dose of morphine, rather than providing evidence of pre-emptive analgesia? It is unclear if the analysis of 24-h postoperative morphine dose included total PCAS requirements in the first 24 h in addition to recovery room analgesic requirements, as no specific information was given on the dose of morphine administered immediately after operation in the recovery room. If 24-h morphine requirements included both recovery room morphine supplements and 24-h PCAS requirements, it is possible that administration of morphine in the recovery room was solely responsible for the significant differences. In theory, pre-emptive analgesia should reduce both immediate postoperative requirements and subsequent PCAS needs. However, a larger dose of morphine without a pre-emptive effect would still reduce immediate postoperative analgesic requirements, although it would not influence later PCAS needs. In order to correctly interpret the statistical analysis of this study, a comparison of immediate analgesic requirements in the recovery room and subsequent 24-h PCAS requirements would be helpful.

The total dose of morphine given in the perioperative period did not differ between the pre-high (63 mg) and pre-low (65 mg) groups. The 24-h postoperative and total postoperative requirements did not differ between the pre-low and post-low groups, and therefore it seems questionable to conclude that pre-emptive morphine reduced postoperative analgesic requirements. We believe the results of this study are consistent with a different interpretation, that is a higher dose of morphine gives better postoperative analgesia than a low dose of morphine. If this is the case then the findings of this study are consistent with those of Collis and colleagues [2] where no significant difference was found in postoperative analgesic requirements in patients who received morphine 10 or 20 mg before operation.

Relative lack of pre-emptive effect of opioids could probably be explained in terms of "*fos* expression" which is a useful marker of the effect of peripheral noxious stimuli on postsynaptic spinal cord neurones. *Fos* expression is not completely suppressed even with a very high dose of systemic morphine, given before onset of nociceptive stimuli, indicating that substantial nociceptive traffic can still occur [3]. There has been a concern that pre-emptive administration of opioids apparently increases pain perception in the late postoperative period [4, 5].

Various randomized controlled trials with NSAID, local anaesthetic block, opioids, including morphine, administered before operation have failed to show any pre-emptive effect on postoperative analgesia [6]. Even multimodal analgesia before surgery did not reduce post-thoracotomy pain or analgesic requirements [7]. However, an NMDA antagonist administered before and after injury has been shown to improve analgesic effect [8] and future clinical trials of pre-emptive analgesia using an NMDA antagonist and morphine would be worthwhile.

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1. Mansfield MD, James KS, Kinsella J. Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements. *British Journal of Anaesthesia* 1996; 76: 358–361.
2. Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? *British Journal of Anaesthesia* 1995; 74: 396–399.
3. Tolle TR, Schadrack J, Castro-Lopez JM, Evan G, Roques BP, Zieglgansberger W. Effects of kelatolorphan and morphine before and after noxious stimulation on immediate early gene expression in rat spinal cord neurones. *Pain* 1994; 56: 103–112.
4. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; 342: 73–75.
5. Wilson RJT, Leith S, Jackson IJB, Hunter D. Preemptive analgesia from intravenous administration of opioids. *Anaesthesia* 1994; 49: 591–593.
6. Dahl JB. The status of pre-emptive analgesia. *Current Opinion in Anesthesiology* 1995; 8: 323–330.
7. Kavanagh BP, Katz J, Sandler AN, Nierenberg H, Roger S, Boylan JF, Laws AK. Multimodal analgesia before thoracic surgery does not reduce postoperative pain. *British Journal of Anaesthesia* 1994; 73: 184–189.
8. Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL, Kissin I. Pre-emptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. *Anesthesia and Analgesia* 1994; 78: 205–209.

Sir,—Thank you for the opportunity to respond to the points raised by Drs Mallick and Dearden. They are correct in stating that patients in the post group (morphine 0.15 mg kg^{-1} on peritoneal closure) received no analgesia other than nitrous oxide until near the end of operation. All patients did, however, receive morphine either before or during surgery, well before awakening after general anaesthesia. In addition, the pattern of analgesic consumption and pain scores do not support the hypothesis that the post group suffered significantly more pain than the two other groups. As this method has been used by other workers, including Richmond and colleagues (reference [4] quoted by Mallick and Dearden), we do not believe there is any ethical dilemma relating to our methodology.

Drs Mallick and Dearden ask if it is possible that our study "indicated that a large dose of morphine provided better analgesia than a small dose, rather than evidence of pre-emptive analgesia". First, we did not demonstrate better analgesia in the pre-high group (although pain scores were consistently lower in this group, the difference between groups was not statistically significant). Second, we were careful not to conclude a pre-emptive analgesic effect from our results. We did conclude that "a large dose of morphine administered on induction of anaesthesia significantly reduced postoperative morphine requirements from a PCA machine compared with a smaller dose given on induction of anaesthesia or at the time of abdominal closure". While it is possible that this is indeed a pre-emptive analgesic effect of a large dose of morphine, we have not tested this hypothesis in our study.

Table 1 shows the amount of morphine administered by us in the recovery ward and PCA morphine use by the patient, from the end of surgery until 24 h after operation.

Table 1 Morphine consumption in the recovery room and PCA morphine use, from the end of surgery until 24 h after operation (median (interquartile range))

	Group		
	Post ($n = 18$)	Pre-low ($n = 22$)	Pre-high ($n = 20$)
Morphine in recovery (mg)	3.5 (0–17.5)	3.0 (0–7.5)	0.0 (0–5.0)
24-h PCA morphine (mg)	61 (51–79)	54 (45–65)	40 (30–49)

While there appears to have been less morphine administered in recovery in the pre-high group compared with the post group, this was not statistically significant ($P = 0.45$, Kruskal–Wallis). As found in the original data analysis, there was a significant difference in the amount of morphine used by patients (PCA) in the pre-high group compared with the post group ($P = 0.0002$) and the pre-low group ($P = 0.0015$, Kruskal–Wallis) but there was no difference between the pre-low and post groups. The suggestion by Mallick and Dearden that the difference in postoperative morphine consumption was caused primarily by an effect in the recovery room is not, therefore, supported.

Finally, we agree with the hypothesis that NMDA antagonists may have a useful role in postoperative pain relief, although this was not tested in our study. Whether they will prove to have a pre-emptive effect remains speculative. It seems unlikely that any single group of analgesic agents will ever be able to abolish pain completely, and that multimodal analgesic strategies are required to optimize postoperative pain relief.

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Convective warming after CABG

Sir,—I read the article of Harrison and Ponte on convective warming [1] with great interest. Have the authors considered the effect of propofol on thermoregulation? It was administered to all patients at a rate of 50–200 mg h^{-1}. Propofol is a well known vasodilator and may have caused vasodilatation in addition to that caused by glyceryl trinitrate. Propofol is also known to attenuate adrenaline and noradrenaline release which would alter the rate of thermogenesis [2]. Was there any significant difference between the dose of propofol administered in each group?

The authors administered glyceryl trinitrate at a rate of at least 15 mg h^{-1} to both control and study patients. As the effect of the Bair Hugger is to cause further vasodilatation, did the authors find that less glyceryl trinitrate was subsequently required in this group compared with the control group, and if so, could this have influenced their results?

The authors dismissed the possibility that large doses of glyceryl trinitrate used in the study accelerated cutaneous heat loss from the control group because of rewarming "at a rate close to that usually observed in the absence of glyceryl trinitrate". It would have been interesting to know how the rate of rewarming in the control group compared with "that usually observed". It appears that peripheral temperatures in the control group were significantly colder during the first 2 h after operation compared with the Bair Hugger group. As heat from the peripheral compartment does not flow up a gradient to the core, it would appear that peripheral cooling could only be caused by loss of heat across the skin to the environment.

The peripheral temperature sites of toe and fingertip may be inaccurate in patients with severe peripheral vascular disease. Were these patients excluded from the study?

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1. Harrison SJ, Ponte J. Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery. *British Journal of Anaesthesia* 1996; **76**: 511–514.
2. Biddle NL, Gelb AW, Hamilton JT. Propofol differentially attenuates the responses to exogenous and endogenous norepinephrine in the isolated rat femoral artery *in vitro*. *Anesthesia and Analgesia* 1995; **80**: 793–799.

Sir,—Our purpose was not to study thermoregulation. For example, in the methods section we stated clearly that thermoregulatory shivering was deliberately abolished; similarly, the doses of glyceryl trinitrate used in both groups were aimed at overcoming physiological mechanisms (thermoregulatory or not) of cutaneous vasoconstriction. The aim of the study was merely to find out if forced warm air could increase the rate of rise of rectal and nasopharyngeal temperature having deliberately minimized thermoregulatory mechanisms, as stated in the discussion section.

The rate of rewarming "usually observed" refers to that observed in most other patients subjected to similar operations in our department, but not included in the study, which is similar to that quoted in references [6, 7 and 16] of our paper. No patient with diabetes or evidence of peripheral vascular disease was included in the study. Apart from the differences between groups described in the results section, there were no other differences in other variables, such as amount of glyceryl trinitrate or propofol infused.

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Adequate general anaesthesia—what are we trying to achieve?

Sir,—Further to the article by Sun, Shyu and Shieh [1] and the accompanying editorial [2], we wish to bring your attention to some relevant findings of studies which were carried out by us in 1995.

We refer in particular to an article on inhibition of nociception-induced spinal sensitization by anaesthetic agents [3]. In this study we sought to determine: (1) if volatile agents reliably block spinal sensitization, (2) if nitrous oxide alone blocks spinal sensitization, (3) if nitrous oxide interferes with the ability of volatile anaesthetics to block sensitization, and (4) if equipotent concentrations of commonly used volatile anaesthetics have different abilities to block sensitization. We found that rats that received halothane, enflurane, isoflurane, desflurane or nitrous oxide during phase 1 of the formalin test demonstrated a significant decrease in phase 2 activity compared with controls, that is suppressed spinal sensitization to pain, with desflurane causing the most suppression. Those rats that received a combination of nitrous oxide and halothane exhibited no difference, that is no suppression was demonstrated.

There is now increasing evidence that volatile anaesthetic agents exert their effect at the spinal cord level [4–7] and this may explain their possible role in pre-emptive suppression of spinal sensitization. There are also many studies which suggest that inhalation anaesthetic agents may suppress nociception in the spinal cord by modifying the activity of NMDA receptors in dorsal horn neurones [8, 9]. While the mechanism by which inhibition of transmission of noxious stimulation by inhalation anaesthetic agents is achieved is still speculative, it has been well documented that they enhance $GABA_A$ mediated sensory inhibition [10–13] and it has been suggested that inhalation anaesthetics may produce suppression of spinal cord sensitization through $GABA_A$ mediated agonism [14].

Some of the analgesic action of nitrous oxide has also been attributed to depressant action on dorsal horn neurones in the spinal cord, perhaps via activation of a supraspinal descending inhibition system. Interestingly, nitrous oxide has been shown to reverse EEG burst suppression provided by isoflurane [15, 16] and desflurane [17], suggesting that it opposes the effect of volatile anaesthetics on the central nervous system. It has also been demonstrated that nitrous oxide has antagonist effects on the MAC of volatile agents [18]. Taken together, these studies indicate that nitrous oxide may antagonize the depressant effects of volatile agents on the central nervous system and this may explain its apparent antagonism of suppression of spinal sensitization by volatile agents in the rat formalin test.

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1. Sun WZ, Shyu BC, Shieh JY. Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin. *British Journal of Anaesthesia* 1996; **76**: 99–105.
2. Munglani R, Fleming BG, Hunt SP. Remembrance of times past: the significance of c-*fos* in pain. *British Journal of Anaesthesia* 1996; **76**: 1–4.
3. O'Connor T, Abram SE. Inhibition of nociception-induced spinal sensitization by anesthetic agents. *Anesthesiology* 1995; **82**; 259–266.
4. Rampil IJ, Mason P, Singh H. Anesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology* 1993; **78**: 707–712.
5. Rampil IJ. Anesthetic potency is not altered after hypothermic spinal cord transection in rats. *Anesthesiology* 1994; **80**: 606–610.
6. Antognini JF, Schwartz K. Exaggerated anesthetic requirements in the preferentially anesthetized brain. *Anesthesiology* 1993; **79**: 1244–1249.
7. Soriano SG, Benthuysen JL, Reitan JA. Minimum alveolar concentration of spinal cord reflexes in rats. *Anesthesiology* 1990; **73**: A705.
8. Namiki A, Collins JG, Kitahata LM. Effects of halothane on spinal neuronal responses to graded noxious heat stimulation in the cat. *Anesthesiology* 1980; **53**: 475–480.
9. Savola MK, Woodley SJ, Maze M. Isoflurane and an A_2-adrenoceptor agonist suppress nociceptive neurotransmission in neonatal rat spinal cord. *Anesthesiology* 1991; **75**: 489–498.
10. Mody I, Tanelian DL, MacIver MB. Halothane enhances tonic neuronal inhibition by elevating intracellular calcium. *Brain Research* 1991; **538**: 319–323.
11. Nakahiro M, Yeh JZ, Brunner E. General anesthetics modulate GABA receptor channel complex in rat dorsal root ganglion neurons. *FASEB Journal* 1989; **3**, 1850–1854.
12. Cheng SC, Brunner EA. Inhibition of GABA metabolism in rat brain slices by halothane. *Anesthesiology* 1981; **55**: 26–33.
13. Cheng SC, Brunner EA. Effects of anesthetic agents on synaptsomal GABA disposal. *Anesthesiology* 1981; **55**: 34–40.
14. O'Connor TC, Abram SE. Possible $GABA_A$ contribution to

suppression of nociceptor induced spinal sensitization. *Regional Anaesthesia* 1994; **19**: 5.

15. Yli-Hankala A, Lindgren L, Porkkala, Jantti V. Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients. *British Journal of Anaesthesia* 1993; **70**: 54–57.
16. Roald OK, Forsman M, Heier MS, Steen PA. Cerebral effects of nitrous oxide when added to low and high concentrations of isoflurane in the dog. *Anesthesia and Analgesia* 1991; **72**: 75–80.
17. Rampil IJ, Lockhart SH, Eger E, Yasuda N, Weiskopf RB, Cahalan MK. The electroencephalographic effects of desflurane in humans. *Anesthesiology* 1991; **74**: 434–439.
18. Cole DJ, Kalichman MW, Sharpiro HM, Drummond JC. The nonlinear potency of sub-MAC concentrations of nitrous oxide in decreasing the anesthetic requirement of enflurane, halothane, and isoflurane in rats. *Anesthesiology* 1990; **73**: 93–99.

Sir,—We thank Drs O'Connor and Abram for their interest in our article [1].

In their letter they highlight the results of their study in which they tested the efficacy of various anaesthetic agents given around the time of formalin administration in inhibiting the subsequent pain-related behaviour, known as the phase 2 formalin response [2]. The phase 2 formalin response consists of complex pain-related behaviour, including licking of and flinching with the affected paw, which occurs 10–60 min after administration of formalin. This latter phase of pain behaviour can be distinguished pharmacologically from the first phase of paw flinching that immediately follows formalin injection into the paw, in that activation of spinal cord NMDA receptor is critical to the second phase, but not first phase of flinching. In contrast, the first phase occurs within the first 5 min of administration of formalin and has been shown to be sensitive to AMPA antagonists. Activation of the NMDA receptor has, in order studies, also been shown to mediate sensitization of individual spinal cord neurones (including "windup") and also to mediate enhancement of spinal cord reflexes [3].

In their study, O'Connor and Abram gave 1 MAC of a volatile anaesthetic agent or 70% nitrous oxide, or propofol (initially 10 mg kg^{-1} and then another 3 mg kg^{-1}, 1 min after formalin) before and during the period of expected phase 1 flinching. They showed that there was suppression of phase 2 flinching with this pre-emptive treatment and so they inferred that spinal cord sensitization had been suppressed (the only exception was that pre-emptive halothane and nitrous oxide given together did not prevent phase 2 flinching). The implications are that conventional anaesthesia does protect the spinal cord during surgery. However, when one looks for other evidence for inhibition of spinal cord sensitization by conventional doses of anaesthetics, the results are conflicting and often depend on the end-point being used. For example, in other studies of formalin-evoked flinching, Abram and Yaksh have shown that even 2.5% isoflurane only reduced phase 2 flinching by 35% when given pre-emptively (and, incidentally, in this study the addition of nitrous oxide to isoflurane abolished this benefit) while intrathecal morphine reduced flinching by 80% [4]. However, in another study, Abram and Olsen found that pre-emptive high-dose systemic opioids did not reduce phase 2 flinching [5]. As for propofol, other studies have not reproduced the findings of O'Connor and Abram [2] in that pre-emptive propofol 10–20 mg kg^{-1} did not reduce phase 2 flinching [6, 7]. Barbiturates similarly show variable efficacy in inhibiting spinal cord sensitization [6–8]. Abram and Yaksh [4] also point out that many of the studies that examined C-fibre induced spinal sensitization were carried out under surgical plane of anaesthesia [9].

Clinical studies have shown that a simple noxious stimulus-evoked reflex in volunteers was inhibited by 0.25–0.5% end-tidal isoflurane. However, repetition (five times at 2 Hz) of the same nociceptive stimulus caused facilitation of the nociceptive reflex and required 1–1.5% isoflurane to suppress it (and the authors pointed out that this dose is similar to the MAC of isoflurane). The authors then suggested that even this higher dose of isoflurane alone would not be adequate for inhibiting surgically evoked excitability in actual operations [10].

Those agents that are generally accepted to produce that state we call anaesthesia were never chosen for their analgesic potential. Several end-points have been used to define an adequate dose of anaesthetic, including loss of consciousness, inhibition of memory formation, lack of intraoperative movement, etc. However, when the results of studies examining more analgesic end-points for conventional anaesthetics are analysed, we find confusing and seemingly contradictory examples, as discussed above. This is because clinically accepted doses of anaesthetics have only moderate ability, at best, to inhibit (i) primary afferent input, (ii) the development of spinal cord sensitization and (iii) short- and long-term pain perception. Fortunately, perhaps conventional anaesthetics do show some analgesic effects, including NMDA receptor blocking activity, but this is unlikely to be contributing to their anaesthetic effect [11].

The purpose of the articles to which O'Connor and Abram refer, is to show that by using immediate early genes as end-points, noxious stimulation still enters the spinal cord during seemingly adequate anaesthesia (see references in [1]). It is not surprising that clinical studies of pre-emptive analgesia show little effect when the agents we use are not particularly good at doing what we ask of them, that is protecting the spinal cord against incoming afferent stimulation. For example it has been demonstrated previously that radically different outcomes in terms of long-term pain behaviour can be produced experimentally with different adjuncts to isoflurane anaesthesia (α_2 agonists, NMDA antagonists, peripheral blocks with local anaesthetic but interestingly, not μ agonists) despite similar lack of responsiveness during anaesthesia [12, 13]. Furthermore, as discussed previously, the ability to suppress *fos* expression by these adjuncts parallels these behavioural outcomes (see references in [1] and also Munglani, Fleming and Hunt, data submitted for publication).

As Abram and Olsen have previously written: "there is a dichotomy between behavioural response to a noxious stimulus and the development of enhanced responsiveness". Furthermore, Abram and Yaksh concluded "that the anesthetised state, as defined by loss of consciousness, or lack of motor response, may be disassociated from the processes leading to post injury facilitation" [4] an observation recently re-emphasized by Goto, Marota and Crosby [14].

As anaesthetists we pride ourselves on producing a state of anaesthesia which includes loss of consciousness, lack of memory formation and minimal autonomic activity. However, the evidence is that conventional anaesthetics (including μ agonists) do not adequately inhibit the longer term consequences of painful stimulation for the patient. Electrophysiological and immediate early gene studies suggest that we need to radically re-think what are our goals for anaesthesia and how we are to achieve them.

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2. O'Connor T, Abram SE. Inhibition of nociception-induced spinal sensitization by anesthetic agents. *Anesthesiology* 1995; **82**: 259–266.
3. Munglani R, Hunt S, Jones JG. Spinal cord and chronic pain. In: Kaufmann L, ed. *Anaesthesia Review*. Edinburgh: Churchill Livingstone, 1996; 53–76.
4. Abram SE, Yaksh TL. Morphine but not inhalational anesthesia blocks post injury facilitation. *Anesthesiology* 1993; **78**: 713–721.
5. Abram S, Olson E. Systemic opioids do not suppress spinal sensitization after subcutaneous formalin in rats. *Anesthesiology* 1994; **80**: 1114–1119.
6. Goto T, Marota JJA, Crosby G. Pentobarbitone, but not propofol, produces pre-emptive analgesia in the rat formalin model. *British Journal of Anaesthesia* 1994; **72**: 662–667.
7. Gilron I, Coderre TJ. Pre-emptive analgesic effect of steroid

anesthesia with alphaxalone in the rat formalin test. *Anesthesiology* 1996; **84**: 572–579.
8. Cleland CL, Lim FY, Gebhart GF. Pentobarbital prevents the development of C-fibre-induced hyperalgesia in the rat. *Pain* 1994; **57**: 31–43.
9. Dickenson A, Sullivan A. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
10. Petersen-Felix S, Arendt-Nielsen L, Bak P, Fischer M, Bjerring P, Zbinden AM. The effects of isoflurane on repeated nociceptive stimuli (central temporal summation). *Pain* 1996; **64**: 277–281.
11. Little HJ. How has molecular pharmacology contributed to our understanding of the mechanism(s) of general anaesthesia? *Pharmacology and Therapeutics* 1996; **69**: 37–58.
12. Munglani R, Bond A, Smith G, Harrison S, Elliot PJ, Birch PJ, Hunt SP. Changes in neuronal markers in a mononeuropathic rat model: relationship between neuropeptide Y, pre-emptive drug treatment and long term mechanical hyperalgesia. *Pain* 1995; **63**: 21–31.
13. Yamamoto T, Shimoyama N, Mizuguchi T. Role of the injury discharge in the development of thermal hyperaesthesia after sciatic nerve constriction in the rat. *Anesthesiology* 1993; **79**: 993–1002.
14. Goto T, Marota JJA, Crosby G. Volatile agents antagonize nitrous oxide and morphine induced analgesia in the rat. *British Journal of Anaesthesia* 1996; **76**: 702–706.

Spinal anaesthesia for Caesarean section

Sir,—We read with interest the letter from Stoneham and Souter on spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia [1]. We congratulate them on their excellent results in 12 such patients, none of whom developed a sensory block above T3. Whether the results in this small series of patients implies that this is a safe technique is still dubious, especially in the face of the frequency of case reports of unexpectedly high spinal block associated with pre-existing extradural block (references [2–7] in Stoneham and Souter's communication).

We take issue with one aspect of their methods. In the list of indications for performing spinal anaesthesia in the presence of a pre-existing extradural block, they included patient(s) in whom the urgency of the situation was considered not to allow time for extension of the extradural block. They then described their technique which involves not preparing the patient for surgery until 20 min after spinal injection. Therefore, the time taken to have the patient ready for surgery is 20 min in addition to the time taken to transfer the patient to theatre, position the patient and perform the spinal anaesthetic. Our technique of choice in this group of patients is to extend the extradural block using an alkalinized mixture similar to that described by Fernando and Jones [2], namely 0.5% bupivacaine 10 ml, 2% lignocaine 10 ml, 1 ml of adrenaline 1 in 10000 (resulting in a final concentration of slightly less than 1 in 200000) and 2 ml of preservative-free 8.4% sodium bicarbonate. Although we have no audit of our own patients on the time taken for extension of the block to an acceptable height, this time is certainly less than 20 min. Using a similar mixture, Fernando and Jones found that the mean time to achieve sensory block T4–S5 in a group of 10 patients was 12.7 min (range 10–14 min) [2]. These patients were undergoing elective Caesarean section and thus had no pre-existing extradural block.

We would advocate the above technique for emergency Caesarean section as it provides suitable surgical anaesthesia without the patient undergoing an additional invasive procedure, that is performance of a spinal anaesthetic and the attendant risks thereof, and achieves this more rapidly than the technique described by Stoneham and Souter.

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1. Stoneham M, Souter A. Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia. *British Journal of Anaesthesia* 1996; **76**: 476.
2. Fernando R, Jones HM. Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural Caesarean section. *British Journal of Anaesthesia* 1991; **67**: 699–703.

Sir,—We read with interest the study by Stoneham and Souter [1]. There is a lack of data on the safety and dose requirements of subarachnoid anaesthesia in women undergoing emergency Caesarean section after extradural analgesia for labour. Therefore, we have recently conducted an audit in order to produce a regimen for the management of these patients in our unit. During the 5-yr period 1990–1994, 30 such patients were identified. There were a variety of reasons for subarachnoid block; 21 cases had inadequate quality of extradural block, the extradural catheter had recently become displaced in eight patients and in the remaining patient there was inadequate time for extension of the extradural. The dose varied between 2 and 3.5 ml of heavy 0.5% bupivacaine, with 17 patients receiving 2.75 ml or more. Four patients also received subarachnoid fentanyl. In 12 cases the injection was given with the patient in the lateral position. We believe the variation in dose and position reflects individual anaesthetist's usual practice. The upper level of the block was recorded in only 16 patients. This varied from T1 to T5, with no correlation with either dose of bupivacaine or position of the patient during injection. In those patients where no block height was recorded, there was no evidence of an abnormally high block. Two of the four patients who received less than 2.5 ml of 0.5% heavy bupivacaine required supplementary analgesia (one general anaesthesia and one alfentanil and nitrous oxide–oxygen). This compared with only two patients requiring supplementation (both alfentanil alone) of the other 26 patients who had received bupivacaine 2.5 ml or more. Three of the four patients requiring additional analgesia had an adequate block height documented before surgery; there was no documented block height recorded for the remaining patient.

As a result of our findings, we have recommended in our unit that patients requiring subarachnoid anaesthesia for Caesarean section after extradural analgesia during labour should have subarachnoid block performed in the anaesthetist's preferred position, using 2.5 ml of heavy 0.5% bupivacaine. Careful attention to positioning, as recommended by Stoneham and Souter, should occur whenever subarachnoid block is given, regardless of whether or not the patient has previously received extradural analgesia. Neither we nor Stoneham and Souter have conclusively demonstrated the safety of the technique and we do not know the incidence of high block, which may be no greater than for subarachnoid block in the absence of pre-existing extradural blocks. We believe, however, unlike the recommendation by Kick and Bohrer [2], that reducing the dose of bupivacaine below our recommendation carries a significant risk of inadequate block.

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1. Stoneham M, Souter A. Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia. *British Journal of Anaesthesia* 1996; **76**: 476.
2. Kick O, Bohrer H. Unexpectedly high spinal anaesthesia following failed extradural anaesthesia for Caesarean section. *Anaesthesia* 1993; **48**: 271.

Sir,—We agree with Drs Foster and Rogers that the technique described by Fernando and Jones of extending an extradural block may be more appropriate than subjecting the patient to the additional risks of a spinal anaesthetic if there is no evidence that the extradural is inadequate. There were two patients in our group of 12 who had unilateral extradural blocks in whom it was felt that there was insufficient time to manufacture a reliable extradural block.

In our limited study, we set out to investigate the unusual situation of women with inadequate extradural blocks who require a regional anaesthetic technique for Caesarean section. Since writing our letter to the *British Journal of Anaesthesia*, there has been further anaesthetic correspondence on this matter [1, 2] recommending that spinal anaesthesia should be avoided under these circumstances until further work has been done. We intended to show that it is possible to perform spinal anaesthesia in patients who have had previous, recent extradural analgesia provided that rigorous care is paid to the positioning of the patient, although of course we are not attempting to suggest that it is safe from the results of studying such small numbers of patients.

The 30 patients described by Drs Vickers and Wilkey are further evidence that it is possible to administer spinal anaesthesia safely in these circumstances, although information on the dose of local anaesthetic, or opioid agents, or both, administered into the extradural space, or how recently they had been given in these 30 patients would have been useful. In addition, we believe that the position of the patient during the siting of the spinal may be less important in determining the outcome than the position of the patient while the spinal anaesthetic develops. Nine of the 10 case reports of unexpectedly high spinal block after failed extradural analgesia were placed in the wedged supine position immediately after spinal injection [3–9]. It is known that the supine hypotensive syndrome is not completely abolished in the wedged supine position [10]. The intriguing possibility arises that partial maternal aortocaval compression in the wedged supine position, leading to extradural venous engorgement, may result in unpredictably high blocks after spinal anaesthesia, particularly where there is already exogenous fluid in the extradural space as in all of these case reports. We are investigating the possibility that positioning patients in the wedged supine position while a spinal anaesthetic is developing may produce a more unpredictable final block height than the lateral position and this may be exacerbated if there is already fluid in the extradural space.

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1. Gupta A. Spinal anesthesia after failed epidural analgesia. *Anesthesia and Analgesia* 1996; **82**: 214.
2. Mets B. Spinal anesthesia after failed epidural analgesia. *Anesthesia and Analgesia* 1996; **82**: 214–215.
3. Stone PA, Thorburn J, Lamb KS. Complications of spinal anaesthesia following extradural block for Caesarean section. *British Journal of Anaesthesia* 1989; **62**: 335–337.
4. Beck GN, Griffiths AG. Failed extradural anaesthesia for caesarean section. Complication of subsequent spinal block. *Anaesthesia* 1992; **47**: 690–692.
5. Dell RG, Orlikowski CE. Unexpectedly high spinal anaesthesia following failed extradural anaesthesia for caesarean section. *Anaesthesia* 1993; **48**: 641.
6. Mets B, Broccoli E, Brown AR. Is spinal anesthesia after failed epidural anesthesia contraindicated for cesarean section? *Anesthesia and Analgesia* 1993; **77**: 629–631.
7. Gupta A, Enlund G, Bengtsson M, Sjoberg F. Spinal anaesthesia for Caesarean section following epidural analgesia in labour: a relative contraindication. *International Journal of Obstetric Anaesthesia* 1994; **3**: 153–156.
8. Goldstein MM, Dewan DM. Spinal anesthesia after failed epidural anesthesia. *Anesthesia and Analgesia* 1994; **79**: 1206–1207.
9. Furst SR, Reisner LS. Risk of high spinal anesthesia following failed epidural block for cesarean delivery. *Journal of Clinical Anesthesia* 1995; **7**: 71–74.
10. Kinsella SM, Lohmann G. Supine hypotensive syndrome. *Obstetrics and Gynecology* 1994; **83**: 774–788.

British Journal of Anaesthesia 1996; 77: 303

BOOK REVIEWS

Regional Anesthesia: An Illustrated Procedural Guide, 2nd Edn. M. F. Mulroy (editor). Published by Little, Brown & Co, Boston. Pp. 313; indexed; illustrated. Price £47.00.

This book aims to provide a practical manual of regional anaesthesia and follows the common pattern of such texts, with the first five chapters dealing with basic physiology and pharmacology, handling of the patient and complications, and equipment. Thereafter specific techniques are discussed individually with explanation of the relevant anatomy and specific complications. The final chapters deal with subspecialty areas, including acute and chronic pain management.

This book is more than just a practical manual. There is a wealth of background information, each chapter is well referenced and all the commonly used regional techniques are covered. The text is well written and easy to follow. The illustrations are mostly black and white with the occasional use of one additional colour. These are certainly adequate for the purpose but no more, and do not compare favourably with other texts. As one might expect, the emphasis is based on North American practice, for example for spinal anaesthesia most of the discussion is about amethocaine, with bupivacaine only mentioned in passing. For i.v. regional anaesthesia the suggested drug is lignocaine and the use of prilocaine or bupivacaine is mentioned. Although the potential problems of the latter are mentioned I would expect stronger criticism in the UK. The book also follows the example of others by including chapters on the use of regional anaesthetic techniques in pain management. This may be appropriate for acute pain, where regional techniques have much to offer, although I did wonder why a section on i.v. patient-controlled analgesia was included. It is less relevant for chronic pain management where regional techniques play a smaller part and other issues such as proper assessment and the decision if and when to use a regional technique assume far greater significance. I hope that these sections in textbooks of regional anaesthesia do not encourage clinicians to dabble in pain management on the basis of ability with a few regional techniques.

There are a large number of up-to-date texts on regional anaesthesia currently available and it will be interesting to see if there really is still a gap in the market. A number of medical texts do not cross the Atlantic well and I think that this will be among them. It is ring bound, presumably so that it can be laid open flat for reference and I hope that this will not encourage self teaching by an individual who is looking at it as the block is performed. I think it unlikely that this format would be suitable for a library or departmental copy as it may not prove very robust. It could not be recommended for trainees and I doubt that it will cope with the competition for a place in departmental libraries, although some enthusiasts for regional anaesthesia may like the style and wish to have their own copy.

W. A. Chambers

ABC of Brainstem Death, 2nd Edn. C. Pallis and D. H. Harley. Published by BMJ Publishing Group, London. Pp. 52; indexed; illustrated. Price £10.95.

The second edition of *ABC of Brainstem Death* has appeared 12 yr after the first. In response to the *Panorama* programme "Transplants: are the Donors Really Dead?" in 1980, a great deal of alarm was spread to the general public, and subsequently, in 1983, the first edition of this text by Christopher Pallis was published. The first edition was an excellent collection of BMJ articles which discussed the definition of death, evolution of thinking towards the concepts of brain death and brainstem death and practical aspects of diagnosis.

The original text has been updated but presented in the same readable fashion with historical, technical and cartoon illustrations which clarify the text. Since that publication it has remained clearly established that no patient in apnoeic coma declared brainstem dead according to the UK criteria ever regained consciousness. Moreover, asystole occurred within a short period of time after the diagnosis was made. This new edition, therefore, has extended considerations of the brainstem dead patient as an organ donor and it also tackles the issue of persistent vegetative state.

UK practice is put into perspective by comparison with approaches to this diagnosis in the rest of the world. The authors correctly observe that the position in the UK is often misunderstood as, despite the endorsement by the Department of Health and the Conference of Medical Royal Colleges and their Faculties, there is no legal status to the UK Code of Practice. The code has never been tested in a court of law, although it has been given tacit support in a House of Lords Select Committee.

The second edition contains useful advice on the management of organ donors and also addresses the issue of elective ventilation. Although many problems are identified, specifically that the Department of Health has accepted legal advice that treatment which is not directly for the patient's benefit may not be lawful, there is no guidance to the reader from the authors on this issue. Perhaps that is why, yet again, this matter has been referred to a Parliamentary Select Committee.

This is an excellent text heartily recommended for all those who are involved with the diagnosis of death and in the management of organ donors.

S. M. Willatts

Recent Advances in Anaesthesia and Analgesia – 19. A. P. Adams and J. N. Cashman (editors). Published by Churchill Livingstone, Edinburgh. Pp. 210; indexed; illustrated. Price £27.95.

The appearance of the 19th in the series of *Recent Advances* is as true a testament to the need for the regular publication of up-to-date reviews of recent developments in our specialty as it is a tribute to the quality of past editions. This latest volume sees a change in editorial personnel, with Dr J. N. Cashman replacing Dr R. S. Atkinson, who was involved with the previous seven, a contribution to which Professor Adams pays full tribute in his foreword.

This edition contains 11 reviews of topical subjects, all clinically relevant, but ranging from very detailed consideration of a small subject (R-R intervals and depth of anaesthesia) to very broad examination of clinical technique (anaesthesia and analgesia for Caesarean section). Each review is commendably concise yet covers the subject comprehensively and is fully referenced. The great majority of authors are UK-based anaesthetists, but one notable exception is Dr R. Green from Farnborough who has contributed a very thought-provoking review on "The psychology of human error", although his numerous references to aviation incidents did make me regret the decision to start reading the book during my plane journey to Sydney for the World Congress!

The commendable brevity, but completeness, of each review, together with the modest price should make this required reading for almost every anaesthetist, and certainly every final fellowship candidate. This does not imply that I do not have criticisms. While one can accept that an expert in a field will be enthusiastic about the subject, I am concerned that the editors should state dogmatically in their preface that "every anaesthetist should be proficient in fibreoptic intubation", particularly as the relevant review admits that this is not the case and recognizes the difficulties. I was also disappointed by the quality of the English in some of the contributions. Style is a matter of preference, and it would be a dull world if we all wrote in exactly the same way, but I cannot consider use of the word "undermedicated" as anything but horrible!

However, these are minor complaints about what is, overall, a very useful volume. The true mark of an expert in any field is that he recognizes what he does not know, and virtually all of the authors are honest with regard to their subjects. It is particularly refreshing to read a review (by Dr D. Justins) of chronic pain that is so honest as to admit that most current therapeutic options are really no more than variations on willow bark and poppy! Buy this book.

J. A. W. Wildsmith

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Complications of hysteroscopic treatments of menorrhagia

Menstrual disorders are extremely common, and approximately 22% of healthy women complain of menorrhagia[1]. However, such complaints are subjective and it is well recognized that many women are poor judges of their menstrual flow. Only 40% of those complaining of heavy periods have menorrhagia, as defined by measured blood losses exceeding 80 ml for each menstruation[2]. This may account in part for the lack of efficacy and patient acceptability of many of the drugs used for the treatment of menorrhagia. Consequently, many patients are referred to gynaecology clinics for surgical management of their problems, menorrhagia accounting for approximately 15% of gynaecological referrals[3].

Before the advent of minimally invasive techniques in the management of menorrhagia, hysterectomy was the surgical treatment of choice; the hysterectomy rate by the age of 55 yr in the UK was approximately 20%[4]. As early as the 1980s there has been increasing enthusiasm for endoscopic techniques aimed at destroying or ablating the endometrium for the treatment of menorrhagia. Three techniques have gained popularity, all using a hysteroscope in conjunction with fluid infused into the uterine cavity under pressure to distend it and give the operator a clear view within the uterus. Electrodiathermy is used in two of the methods, with the endometrium being resected with a wire loop (resection) or ablated with a "rollerball" (coagulation). For the third technique a Nd-YAG laser is used to ablate the endometrium. Although the three techniques destroy the endometrium in different ways, collectively they are termed transcervical endometrial ablation (TCEA).

In comparison with hysterectomy, hysteroscopic techniques are simple, require less operating time and the time for the patient to recover fully is substantially reduced. However, there is concern that some serious complications may occur during hysteroscopic surgery and it is important that both surgeons and anaesthetists are aware of this morbidity, especially as many of these procedures take place as day-cases. The main complications of TCEA are postoperative haemorrhage, fluid absorption, infection and uterine perforation.

Postoperative haemorrhage occurs in up to 2.5% of cases[5–7], occasionally being severe enough to require blood transfusion. Haemostasis may be produced by inserting a Foley catheter into the uterine cavity and inflating the balloon to compress the vessels—usually a period of 4–8 h is adequate.

Fluid overload is a potentially serious complication of TCEA. Absorption of excessive amount of irrigation fluid during operation directly through blood vessels opened up by the resection may lead to the syndrome familiar to urologists and anaesthetists as transurethral resection of the prostate (TURP) syndrome. Fluid entering the peritoneal cavity though patent Fallopian tubes may also be absorbed into the circulation but the magnitude or significance of this fluid absorption is not clear. One study has shown a 20% reduction in fluid absorption in women with occluded Fallopian tubes caused by prior sterilization[8]. The incidence of fluid overload (defined as losses exceeding 2000 ml) in TCEA varies from 1 to 5%[9–11]. The development of fluid overload is influenced by several factors, including type of irrigation fluid, infusion pressure, vascularity of the uterus, duration of surgery and surgical technique.

Electrodiathermy requires the use of solutions which do not conduct electricity. These include 1.5% glycine, 5% sorbitol and 5% mannitol[12]. The most commonly used irrigation fluid is 1.5% glycine. It has good optical qualities but is hypotonic (osmolality of 1.5% glycine is 188 mosmol kg^{-1}) and absorption into the circulation may cause fluid overload, hyponatraemia, pulmonary oedema and cerebral oedema. Hyperglycinaemia and hyperammonaemia may occur with the use of 1.5% glycine. Hyperglycinaemia has been reported as the cause of transient blindness in some patients undergoing TURP[13 14]. Glycine is broken down in the liver into ammonia and oxalate; ammonia may produce deterioration of cerebral function after endometrial ablation when the blood concentration of ammonia exceeds 150 μmol litre^{-1} (normal 11–35 μmol litre^{-1})[15 16]. In addition, transient arterial oxygen desaturation, hypercapnia and coagulopathy have been reported[17].

Sorbitol 5% is isotonic with a short half-life of 35 min but it causes toffee-like deposits on the electrode and this may make the resection technically difficult. Consequently, it is seldom used. Mannitol 5%, although isotonic, has a long half-life and is also seldom used; it may cause visual distortion and crystallization on instruments[18]. Normal saline may be used only when laser treatment is contemplated and there is no danger of electrical conduction. It is isotonic and optically clear but it may also lead to fluid overload and pulmonary oedema if absorbed in large quantities. Carbon dioxide may be used for distension during diagnostic hysteroscopy, but although excellent vision is provided, it cannot be used in conjunction with operative hysteroscopy as these procedures open vessels through which carbon dioxide can gain access to the circulation and cause pulmonary embolus[18]. Production of smoke during resection may also impair vision when carbon dioxide is used for distension.

The uterine cavity has a low compliance and high irrigation pressures are required during endometrial ablation. Although views of the uterine cavity are possible with irrigation pressures of 40 mm Hg, it has been shown that pressures of 100–110 mm Hg may be required to see the tubal orifices[19]. The intrauterine pressure (IUP) attained during endometrial laser ablation may influence the amount of fluid absorbed and it has been suggested that this should be limited to 60 mm Hg[20]. Various methods are used to introduce fluid into the uterine cavity under some type of pressure control. The simplest method uses a gravity fed system. This consists of a 3-litre bag containing fluid and held 1 m above the uterus, thus providing sufficient pressure for uterine distension. Pressurizing the infusion bag is an alternative and relatively cheap method of controlling uterine pressure. Peristaltic pumps, although considerably more expensive, have been used widely to provide constant flow. These give excellent visual conditions but may be associated with a progressive increase in IUP. With such constant flow variable pressure pumps, excess fluid absorption is a particular problem. This problem can be reduced by using pressure controlled pumps[21]. In a study by Hasham and colleagues[22], a hysterogram was obtained during endometrial laser ablation and this showed no absorption of irrigation fluid into the venous system at an IUP of 70 mm Hg, while at 150 mm Hg contrast medium was seen entering the uterine venous system.

Less absorption of fluid may occur if resection takes place when the endometrium is relatively avascular, hence it is preferable to carry out this procedure during the mid-proliferative phase of the menstrual cycle. Some gynaecologists prefer to prescribe some type of hormonal preparation with danazol, progestogen or gonadotrophin-releasing hormone (GnRH) agonists to make the endometrium atrophic[20 23].

Absorption of fluid may be influenced by the duration of the resection. It has been suggested that reduction of operating time to 1 h or less may minimize the development of TURP syndrome. However, as with TURP syndrome, the risk of developing fluid overload in TCEA is not always related to the duration of surgery; the syndrome may develop in 10–15 min[24 25]. Surgical technique also influences the development of fluid overload. Of the three methods used, endometrial rollerball coagulation carries least risk[26] as there is no cutting of blood vessels or tissue and thus there is less fluid absorption and haemorrhage compared with the two other techniques.

The amount of fluid absorbed by the patient may be calculated as the volume of fluid infused into the uterine cavity minus the volume which passes out through the cervix into the collection system and on to drapes and swabs. This is defined as the fluid deficit. It is important to monitor fluid deficit continuously in order to provide an early estimation of the rate of fluid absorption. Unfortunately, there is no simple, accurate method of measuring fluid deficit, although volumetric and gravimetric methods are commonly used. In the simple volumetric method, the difference between the volume of irrigation fluid used and the volume recovered is measured. A more complex but accurate volumetric method has been described by Hahn, Berlin and Lewenhaupt[27]; in this method 3-litre bags are weighed accurately before and after use. During hysteroscopy they are placed 60 cm above the centre of the surgical field. The first bag is used to fill the irrigation system before the operation is started. A volumetric irrigating fluid balance is obtained every 10 min during operation: the irrigation fluid inlet is closed, the uterus emptied and the irrigating fluid bag and the collecting bag replaced. Blood loss is calculated from the haemoglobin concentration of the irrigation fluid. Because this method is complex, it is less applicable to routine use and is more useful for research. In contrast, the gravimetric method is simple in concept but involves weighing the patient either on the operating table or the bed[28] and is therefore cumbersome and rarely used.

In 1991, Hulten and colleagues described a simple, non-invasive and continuous method of monitoring irrigation fluid absorption during TURP using ethanol[29]. The irrigation fluid is tagged with ethanol and expired breath ethanol concentration measured using an alcohol analyser. Glycine 1.5% with 1% ethanol (Baxter Health Care Ltd, UK) is available in the UK. Blood ethanol concentrations reflect the balance between the rate of entry into the circulation and the rate of removal, redistribution and elimination. Nomograms have been developed which relate ethanol concentration in expired gas to the volumes of irrigant fluid absorbed and the resulting reduction in serum sodium concentration during TURP surgery. The same evaluations of correlations between expired ethanol concentration, serum sodium concentration and volume of irrigant absorbed have also been made in 62 patients undergoing TCEA[28 30]. Using these nomograms it was found that the volume of irrigant absorbed during TCEA produced about a 10% greater increase in expired ethanol concentration and a 40% greater reduction in sodium concentration than occurs during TURP. It is difficult to account for these differences and clearly a larger bank of data is required in order to develop nomograms for patients undergoing endometrial ablation. At present, therefore, fluid deficit is the best indicator of fluid overload during TCEA. It is recommended that surgery is stopped as soon as possible when the deficit is 1000–2000 ml and immediately when the deficit exceeds 2000 ml[31]. Some authors have suggested that when a 500-ml deficit is noted, serum electrolyte concentrations should be measured to check sodium concentrations and if a 1000 ml deficit occurs, frusemide 20 mg should be administered i.v.[18].

The syndrome arising from absorption of large volumes of irrigation fluid has been described and studied extensively in relation to TURP syndrome[32 33]. Circulatory overload may cause acute left ventricular failure, pulmonary oedema and hypoxia. Hyponatraemia causes cerebral oedema; if the serum sodium concentration decreases to less than 120 mmol litre^{-1}, agitation, nausea, vomiting, headaches and confusion usually occur and subsequently there may be seizures, coma, respiratory arrest and even death[34]. Plasma sodium concentration and osmolality should be monitored closely if clinical signs occur suggestive of the syndrome. As a guide to clinical management it has been suggested that a serum sodium concentration of 120 mmol litre^{-1} be the boundary between mild and severe hyponatraemia[33]: mild hyponatraemia should be treated with fluid restriction and diuretics. Although 3–5% hypertonic saline 200–500 ml over 4 h has been recommended[35] for the treatment of severe hyponatraemia, there is concern about its use. If hyponatraemia is corrected too rapidly, it may lead to an abrupt decrease in cerebral blood volume leading to intracranial haemorrhage[36]. Excessively rapid correction of chronic hyponatraemia may cause cerebral demyelination lesions (central pontine myelinolysis)[37]; however, the pathophysiology of this syndrome differs from that of acute hyponatraemia and demyelinating lesions have not yet been described in either the TURP[32] or TCEA syndrome. Diagnosis of hyponatraemia during anaesthesia is aided by development of electrocardiographic changes such as wide QRS complexes and ST-elevation, progressing to ventricular tachycardia and ventricular fibrillation[32].

Although it is standard practice to use prophylactic antibiotics, postoperative infection occurs in up to 2% of patients undergoing TCEA; this rate is substantially less than that in women undergoing hysterectomy[38]. Uterine perforation complicates up to 4% of endometrial resections[7–11] but this may be less with the laser than the wireloop or rollerball techniques[5]. In most reports, perforation has occurred during insertion of either a sound or endoscope through the cervix. Such perforations are unlikely to lead to damage of other structures provided the complication is recognized and the procedure is abandoned. If perforations occur while the laser or diathermy is in use there may be damage to large vessels, bladder or bowel. If such damage is feared, laparotomy is usually necessary rather than laparoscopy as the latter may not easily reveal the site of any damage.

There have been three randomized controlled trials comparing hysteroscopic methods of managing menorrhagia with abdominal hysterectomy[11 38 39]. All reported substantially decreased operating times for the hysteroscopic methods, and an average hospital stay of 1 day compared with 7 days for hysterectomy. Time to full recovery (defined as time taken to return to work) was 2–3 weeks compared with 2–3 months for the hysterectomy group. Complications were significantly fewer in the endoscopic group, with 4–8% of patients developing complications compared with 46% of the hysterectomy group[11]. However, in one study, long-term follow up revealed that women undergoing hysterectomy were generally more satisfied with treatment; 89% of patients were satisfied compared with 78% in the endoscopic group[40]. Of those allocated to hysteroscopic treatment, 12% required repeated endoscopic treatment for continued menorrhagia and 16% required hysterectomy within 2 yr. Analysis of the cost-benefit ratio was undertaken in this study[40]; at 4 months endoscopic therapy as a percentage of mean total cost of hysterectomy was 53%, but by 2 yr, taking into account additional therapy, the gap had narrowed to 71%. Longer term follow-up is awaited to determine if the cost benefit of endoscopic therapy persists.

Although the benefits of endometrial ablation both to the patient and in financial terms are unclear, there is no doubt that hysteroscopic techniques for managing menorrhagia are increasingly popular with both patients and gynaecologists. However, these techniques are still in an evolutionary stage. Most TCEA procedures are performed as day-cases and it is important for anaesthetists to be aware of the immediate complications that can occur. Patients who are at risk of developing complications should be admitted for observation as inpatients. While complications are uncommon after the patient leaves hospital, it is important that the patient and general practitioners are fully aware of potential late problems.

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References

1. Gath D, Osborne M, Bungay G, Iles S, Day A, Bond, Passingham C. Psychiatric disorder and gynaecological symptoms in middle aged women: a community survey. *British Medical Journal* 1987; **294**: 213–218.
2. Fraser IS, McCarron G, Markham R. A preliminary study of factors influencing perception of menstrual blood loss volume. *American Journal of Obstetrics and Gynecology* 1984; **149**: 788–793.
3. Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice. *British Journal of Obstetrics and Gynaecology* 1991; **98**: 789–796.
4. Vessey M, Villard-Mackintosh L, McPhearson K, Coulter A, Yeates D. The epidemiology of hysterectomy: findings in a large cohort study. *British Journal of Obstetrics and Gynaecology* 1992; **99**: 402–407.
5. Magos AL, Baumann R, Turnbull AC. Transcervical resection of the endometrium in women with menorrhagia. *British Medical Journal* 1989; **298**: 1209–1212.
6. Garry R, Erian J, Grochmal S. A multi-centre collaborative study into the treatment of menorrhagia by Nd-YAG laser ablation of the endometrium. *British Journal of Obstetrics and Gynaecology* 1991; **98**: 357–362.
7. Pyper R, Haeri A. A review of 80 endometrial resections for menorrhagia. *British Journal of Obstetrics and Gynaecology* 1991; **98**: 1049–1054.
8. Magos AL, Baumann R, Turnbull AC. Safety of transcervical endometrial resection. *Lancet* 1990; **i** : 44.
9. Magos AL, Baumannn R, Lockwood GM, Turnbull AC. Experience with the first 250 endometrial resections for menorrhagia. *Lancet* 1991; **337**: 1074–1078.
10. Sturdee D, Hoggart B. Problems with endometrial resection. *Lancet* 1991; **337**: 1474.
11. Dwyer N, Hutton J, Stirrat GM. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for surgical treatment of menorrhagia. *British Journal of Obstetrics and Gynaecology* 1993; **100**: 237–243.
12. Holt EM, Gillmer MDG. Endometrial resection. In: Gordon AG, ed. *Baillière's Clinical Obstetrics and Gynaecology.* London: Baillière Tindall, 1995; **9**: 279–297.
13. Wang JML, Creel DJ, Wong KC. Transurethral resection of the prostate, serum glycine levels and ocular evoked potentials. *Anesthesiology* 1989; **70**: 36–41.
14. Ovassapian A, Joshi CW, Brunner EA. Visual disturbance: an unusual symptom of transurethral prostatic resection reaction. *Anesthesiology* 1982; **57**: 332–334.

15. Roesch RP, Stoeling RK, Lingeman JE, Kahnoski RJ, Backes DJ, Gephardt SA. Ammonia toxicity resulting from glycine absorption during a transurethral resection of the prostate. *Anesthesiology* 1983; **58**: 577–579.
16. Kirwan PH, Ludlow J, Makepeace P, Layward E. Hyperammonaemia after transcervical resection of the endometrium. *British Journal of Obstetrics and Gynaecology* 1993; **100**: 603–604.
17. Goldenberg M, Zolti M, Seidman DS, Bider D, Mashiach S, Etchin A. Transient blood oxygen desaturation, hypercapnia, and coagulopathy after operative hysteroscopy with glycine used as the distending medium. *American Journal of Obstetrics and Gynecology* 1994; 170: 25–29.
18. Ananthanarayan C, Paek W, Dhanidina K. Hysteroscopy and anaesthesia. *Canadian Journal of Anaesthesia* 1996; 43: 56–64.
19. Quinones RG. Hysteroscopy with a new fluid technique. In: Siegler AM, Lindemann HJ, eds. *Hysteroscopy. Principals and Practise*. Philadelphia: Lippincott, 1984; 41–42.
20. Boto TC, Fowler CG, Cockcroft S, Djahanbakch O. Absorption of irrigating fluid during transcervical resection of endometrium. *British Medical Journal* 1990; **300**: 748.
21. Garry R. Endometrial laser ablation. In: Gordon AG, ed. *Baillière's Clinical Obstetrics and Gynaecology*. London: Baillière Tindall, 1995; 9: 317–328.
22. Hasham F, Garry R, Kokri MS, Mooney P. Fluid absorption during laser ablation of the endometrium in the treatment of menorrhagia. *British Journal of Anaesthesia* 1992; **68**: 151–154.
23. Sutton CJG, Ewer SP. Thinning the endometrium prior to ablation: is it worthwhile? *British Journal of Obstetrics and Gynaecology* 1994; **101**(Suppl. 10): 10–12.
24. McSwiney M, Myatt J, Hargreaves M. Transcervical endometrial resection syndrome. *Anaesthesia* 1995; **50**: 254–258.
25. Istre O, Skajaa K, Schjoensby AP, Forman A. Changes in serum electrolytes after transcervical resection of the endometrium and submucous fibroids with use of glycine 1.5% for uterine irrigation. *Obstetrics and Gynecology* 1992; **80**: 218–222.
26. Valle RF. Rollerball endometrial ablation. In: Gordon AG, ed. *Baillière's Clinical Obstetrics and Gynaecology*. London: Baillière Tindall, 1995; 9: 299–315.
27. Hahn RG, Berlin T, Lewenhaupt A. Irrigating fluid absorption and blood loss during transurethral resection of the prostate studied by regular interval monitoring (RIM) method. *Scandinavian Journal of Urology and Nephrology* 1988; **22**: 23–30.
28. Hahn RG. Ethanol monitoring of irrigating fluid absorption. *European Journal of Anaesthesiology* 1996; **13**: 102–115.
29. Hulten J, Sarma VJ, Hjertberg H, Palmquist B. Monitoring of irrigation fluid absorption during transurethral prostatectomy. A study in anaesthetised patients using 1% ethanol tag solution. *Anaesthesia* 1991; **46**: 349–353.
30. Olsson J, Hahn RG. Ethanol monitoring if irrigation fluid absorption in transcervical endometrial resection of the endometrium. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 252–258.
31. Magos AL. Endometrial ablation for menorrhagia. In: Studd J, ed. *Progress in Obstetrics and Gynaecology*, Edinburgh: Churchill Livingstone, 1991; **9**: 375–395.
32. Jensen V. The TURP syndrome. *Canadian Journal of Anaesthesia* 1991; **38**: 90–97.
33. Hatch PD. Surgical and anaesthetic consideration in transurethral resection of the prostate. *Anaesthesia and Intensive Care* 1987; **15**: 203–211.
34. Arieff AI, Ayus JC. Endometrial ablation complicated by fatal hyponatremic encephalopathy. *Journal of the American Medical Association* 1993; **270**: 1230–1232.
35. Hahn RG. The transurethral resection syndrome. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 557–567.
36. Alvis R, Geheb M, Cox M. Hypo- and hyper-osmolar states: diagnostic approaches. In: Arieff AI, De Fronza RA, eds. *Fluid, Electrolyte and Acid-base Disorders*. New York: Churchill Livingstone Inc, 1985; 185–219.
37. Sterns RH, Riggs JE, Schochet SS. Osmotic demyelination syndrome after correction of hyponatremia. *New England Journal of Medicine* 1986; **314**: 1535–1542.
38. Pinion S, Parkin D, Abramovich D, Nayi A, Alexander A, Russell I, Kitchener H. Randomised trial of hysterectomy, endometrial laser ablation and transcervical resection for dysfunctional uterine bleeding. *British Medical Journal* 1994; **309**: 979–983.
39. Gannon M, Holt E, Fairbank J, Fitzgerald M, Milne M, Crystal A, Green. Randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. *British Medical Journal* 1991; **303**: 1362–1364.
40. Sculper M, Dwyer N, Byford S, Stirrat G. Randomised trial comparing hysterectomy and transcervical resection: effect on health related quality of life and costs two years after surgery. *British Journal of Obstetrics and Gynaecology* 1996; **103**: 142–149.

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EDITORIAL II

What future is there for predicting difficult intubation?

With the publication of another study on the accuracy of clinical bedside tests to predict difficulty with intubation[1] it is perhaps reasonable to question what impact these studies have had on our understanding of difficult intubation and what lies in the future in this field. One of the problems with many of these studies it that there has been a lack of reproducibility and perhaps a tendency to modify the tests accordingly. Because of the diversity of factors involved, the desire to have a simple bedside test to predict almost all cases of difficulty may be considered unduly optimistic. Presumably, Wilson and colleagues started with this hope when they proposed a scheme specifically to assess a combination of factors[2]. Another major problem in this area is the lack of universal agreement on what is implied by "difficult"[3].

Bellhouse and Doré[4] derived a predictive formula based on a retrospective radiological survey of subjects who presented difficulty in tracheal intubation. More importantly, they claimed that the most important features relevant to difficulty were reduced atlanto–occipital extension, reduced mandibular space and increased anteroposterior thickness of the tongue. Recent studies have focused most attention on the Mallampati test[5], thyromental distance[6] and sternomental distance[7]. The Mallampati test involves the relative size of the tongue by observation of the degree to which it appears to fill the mouth (i.e. obscure the view of the soft palate). The two other tests fit with the concept of space for the tongue within the constraints of the mandible and the degree to which the airway is opened by adequate extension of the neck. Many studies have supported their individual or combined efficacy[8–11], but each test has also been questioned or received only qualified support by others[1–3 12–14]. Reproducibility of the Mallampati test in particular has been questioned and the relevant issues were well reviewed in the study of Pilkington and colleagues who made photographic assessments for Mallampati gradings during pregnancy[15].

While clinical studies on prediction of difficulty in intubation have been published on a regular basis, a parallel branch of clinical and theoretical research has continued, following on from another aspect of Bellhouse's work, that is to further understand and model the mechanisms of difficulty[16–20]. This culminated in a two-dimensional mathematical model for osseous factors in difficult intubation[21]. At the time it was thought that verification of this model would be daunting. The main principle for appropriate use of the traditional Macintosh laryngoscope is negotiation of the curved blade around and beyond the base of the tongue to make contact with the hyoid bone in order to elevate the epiglottis. The hyoid can be lifted forward if the blade tip is at least in contact with the lesser horns of they hyoid, but shortening of the hyoepiglottic ligament maximizes elevation of the epiglottis and this is achieved when the blade tip is directly behind the body of the hyoid and particularly when it is below this level[16]. Apart from when there is severely limited mouth opening, the usual obstruction to adequate exposure of the larynx is the tongue[4].

From the point of view of the two-dimensional model, the main considerations are the relative alignment of two intersecting straight lines[21]. The first line extends from the tip of the upper incisors to an anterior airway point immediately above the laryngeal inlet and may be considered to represent the optimal natural eyeline. The second is also in the median plan and represents the jaw as an imaginary line from the internal midpoint of the symphysis of the mandible to an imaginary point midway between the condyles. The relationship between these lines can be used to describe anatomical variations and also dynamic changes which occur on mouth opening or change in head and neck position, or both. A "final common pathway" for most causes of difficulty with intubation has been suggested to be the relative lack of space into which the tongue remaining anterior to the laryngoscope blade (the "minimal residual volume") can be displaced in order to view the larynx[19]. This space is represented in the model by the triangle demarcated by the jaw line superiorly and the optimal natural eyeline posteriorly. When this space is severely restricted, attempts to perform conventional laryngoscopy with a Macintosh blade have been shown to force the tongue down into the pharynx with the result that the epiglottis can become fixed against the posterior pharyngeal wall. This has been termed the "peardrop effect", on the basis of the way in which the minimal residual volume becomes distorted under these circumstances. In this context the actual laryngoscopy blade used is important and an appropriate analysis of the blade shape was suggested by Marks, Hancock and Charters[22].

There is a paradox in many of these considerations in that, to anaesthetists who regularly deal with the most difficult intubations in their routine clinical practice, much of what has already been described is fairly irrelevant. Dealing with tumours of the supraglottic region and base of tongue represents the most challenging intubation problem and yet it is very unlikely that predictions of degree of difficulty for such cases would be fruitful. Even benign soft tissue problems such as vallecula cysts may cause severe laryngoscopic embarrassment because they interfere with the usual mechanism of laryngoscopy (i.e. the blade tip must enter the vallecula) or push the epiglottis posteriorly, making it difficult to reposition the blade tip below the epiglottis to lift it up. These patients tend to be asymptomatic even when the cysts are fairly large[23]. Radiation changes may also have an important effect in decreasing soft tissue mobility but the history and preoperative clinical findings should indicate the likely effect in these cases. Stylohyoid ligament calcification is another unusual cause of difficulty but it is important in understanding the mechanisms of intubation as it limits forward movement of the hyoid which is required to elevate the epiglottis[19]. The prediction tests would not be expected to be sensitive to these uncommon but important conditions nor would the mathematical model, but then the model specifically describes osseous factors only.

An important discovery with the intubation model was the prediction of a previously unreported mechanism of difficulty termed the "hi-slung mandible". With respect to intubation, it is the lower compartment of the temporomandibular joint which needs to be considered because the condyles are naturally in this position when the mouth opens and when the laryngoscope is pulling the hyoid forward. In the condition of "hi-slung mandible", the temporomandibular joint is abnormally anterior and rostral. When a patient is positioned in the "standard intubating position"[17] with the laryngoscope exposing the larynx, the optimal natural eyeline and jaw line intersect at approximately 90° [21]. This implies that if the jaw is considered to simply rotate around the condyles (given that it is already in the lower compartment of the temporomandibular joint), the jaw line is as far in front of the natural optimal eyeline as possible. On the other hand, if the centre of rotation is higher and more anterior than normal, as with the "hi-slung mandible", opening the jaw sufficiently to admit a laryngoscope blade will ensure that the jaw line/optimal natural eyeline intersection is significantly less than 90°. Therefore, even if jaw translation appears normal with the mouth closed, the act of mouth opening in this condition makes the jaw fall back markedly so as to make it behave as if it were receded. The incidence of this phenomenon is unknown but examples have been cited and it may not be very uncommon. It would be expected that the currently popular predictive tests would not recognize this problem.

One unfortunate feature of most of the studies which have attempted to predict difficulty in intubation appear to be the inability to explain failures. This is perhaps understandable because of the requirement to examine large numbers of subjects in order to determine low failure rates and false positive predictions. This deficiency has been commented on previously[24]. The most important lesson from the intubation model is that factors combine to produce a net effect and it may be that adverse effects are counterbalanced to a greater effect by favourable ones. For example, absent upper incisors may make a severely receded jaw less of a problem but if prominent buck teeth occur in the presence of a receded jaw, the effect is likely to be considerably worse. In the model, this net effect on expected laryngeal exposure is measured as an "F" score which is directly related to the area of the triangular space below the mandible, as described above.

Bellhouse also described a new blade[25]. This was the first blade design to be related specifically to measurements and ideas derived from an analytical clinical study. The study on the function of various blade shapes by Marks, Hancock and Charters[22] was essentially descriptive but could be converted relatively easily to a computational form. It remains to be seen if this approach challenges further the position of the Macintosh blade as the optimal rigid design. At present the future for simple predictive bedside tests is speculative. It is clear from all the published work over the past decade that our understanding of the mechanisms of tracheal intubation have advanced substantially. As far as modelling is concerned, the future holds great potential. Three-dimensional computer imaging is already in existence and it may only be a short time before routine preoperative imaging of ENT/facio-maxillary patients can be presented to the anaesthetist in a virtual reality setting in which various alternative intubation techniques can be tried by simulation before taking the patient to the operating theatre.

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References

1. Ramadhani SAL, Mohamed LA, Rocke DA, Gouws E. Sternomental distance as the sole predictor of difficult laryngoscopy in obstetric anaesthesia. *British Journal of Anaesthesia* 1996; 77: 312–316.
2. Wilson ME, Spieghalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; **61**: 211–216.
3. Rose DK, Cohen MM. The airway: problems and predictions in 18,500 patients. *Canadian Journal of Anaesthesia* 1994; **41**: 372–383.
4. Bellhouse CP, Doré C. Criteria for estimating likelihood of difficulty of endotracheal intubation with the Macintosh laryngoscope. *Anaesthesia and Intensive Care* 1988; **61**: 329–337.
5. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraska B, Freiberger D, Liu PL. A clinical sign to predict difficult tracheal intubation: A prospective study. *Canadian Journal of Anaesthesia* 1985; 32: 429–434.
6. Patil VU, Stehling LC, Zaunder HL. *Fibre-optic Endoscopy in Anaesthesia*. Chicago: Year Book Medical Publishers, 1983.
7. Savva D. Prediction of difficult tracheal intubation. *British Journal of Anaesthesia* 1994; 73: 149–153.
8. Samsoon GLT, Young JRB. Difficult intubation: a retrospective study. *Anaesthesia* 1987; 42: 487–490.
9. Frerk CM. Predicting difficult intubation. *Anaesthesia* 1991; 46: 1005–1008.
10. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. *Anesthesiology* 1992; 77: 67–73.
11. Calder I, Calder J, Crockard HA. Difficult direct laryngoscopy in patients with cervical spine disease. *Anaesthesia* 1995; 50: 756–763.
12. Oates JDL, Macloed AD, Oates PD, Pearsall FJ, Howie JC, Murray GD. Comparison of two methods for predicting difficult intubation. *British Journal of Anaesthesia* 1991; **66**: 305–309.
13. Butler PJ, Dhara SS. Prediction of difficult laryngoscopy: an assessment of the thyromental distance and Mallampati predictive tests. *Anaesthesia and Intensive Care* 1992; **20**: 139–142.
14. Lewis M, Keramati S, Benumof JL, Berry CC. What is the best way to determine oropharyngeal classification and mandibular space length to predict difficult laryngoscopy? *Anesthesiology* 1994; **81**: 69–75.
15. Pilkington S, Carli F, Dakin MJ, Romney M, De Witt KA, Doré CJ, Cormack RS. Increase in Mallampati score during pregnancy. *British Journal of Anaesthesia* 1995; 74: 638–642.
16. Horton WA, Fahy L, Charters P. Position of tip of Macintosh blade during laryngoscopy. *British Journal of Anaesthesia* 1988; **61**: 109P.
17. Horton WA, Fahy L, Charters P. Defining a standard intubating position using "Angle Finder". *British Journal of Anaesthesia* 1989; 62: 6–12.
18. Horton WA, Fahy L, Charters P. Disposition of cervical vertebrae, atlantoaxial joint, hyoid and mandible during x-ray laryngoscopy. *British Journal of Anaesthesia* 1989; **63**: 435–438.

19. Horton WA, Fahy L, Charters P. Factor analysis in difficult tracheal intubation: laryngoscopy-induced airway obstruction. *British Journal of Anaesthesia* 1990; **65**: 801–805.
20. Fahy L, Horton WA, Charters P. Factor analysis in patients with a history of failed tracheal intubation during pregnancy. *British Journal of Anaesthesia* 1990; **65**: 813–815.
21. Charters P. Analysis of mathematical model for osseous factors in difficult intubation. *Canadian Journal of Anaesthesia* 1994; 41: 594–602.
22. Marks RRD, Hancock R, Charters P. An analysis of laryngoscope blade shape and design: new criteria for laryngoscope evaluation. *Canadian Journal of Anaesthesia* 1993; **40**: 262–270.
23. Mason DG, Wark KJ. Unexpected difficult intubation. Asymptomatic epiglottic cysts as a cause of upper airway obstruction during anaesthesia. *Anaesthesia* 1987; **42**: 407–410.
24. King TA, Adams AP. Predicting difficult intubation. What factors influence the thyromental distance? *British Journal of Anaesthesia* 1992; **47**: 623
25. Bellhouse CP. An angulated laryngoscope for routine and difficult tracheal intubation. *Anesthesiology* 1988; **69**: 126–129.

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CLINICAL INVESTIGATIONS

Sternomental distance as the sole predictor of difficult laryngoscopy in obstetric anaesthesia

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Summary

Sternomental distance and view at laryngoscopy were documented in 523 parturients undergoing elective or emergency Caesarean section under general anaesthesia. Eighteen (3.5%) had a grade III or IV laryngoscopic view (Cormack and Lehane's classification) and were classified as potentially difficult tracheal intubations. There was a significant difference between sternomental distance in those patients with a grade III or IV laryngoscopic view compared with those with a grade I or II (13.17 (SD 1.54) cm *vs* 14.3 (1.49) cm; P=0.0013). A sternomental distance of 13.5 cm or less with the head fully extended on the neck and the mouth closed provided, using discriminant analysis, the best cut-off point for predicting subsequent difficult laryngoscopy. A sternomental distance of 13.5 cm or less had a sensitivity, specificity, positive and negative predictive values of 66.7%, 71.1%, 7.6% and 98.4%, respectively. While there was no association between sternomental distance and age, weight, height or body mass index (BMI), there was a significant association between grade of laryngoscopy (III and IV) and older (P=0.049) and heavier (P=0.0495) mothers. The results suggest that while sternomental distance on its own may not be an adequate sole predictor of subsequent difficult laryngoscopy the measurement should be incorporated into a series of quick and simple preoperative tests. (*Br. J. Anaesth.* 1996;**77**:312–316)

Key words

Anaesthesia, obstetric. Anaesthetic techniques, laryngoscopy. Larynx, laryngoscopy. Intubation tracheal, difficult.

The most recent Report on Confidential Enquiries into Maternal Deaths in the UK has continued to highlight the relationship between maternal death and difficulty with tracheal intubation[1]. Because of the potentially serious consequences of failed tracheal intubation, considerable attention has focused on attempts to predict, at the preoperative assessment, patients in whom laryngoscopy and intubation will be difficult[2–8]. Only one of these studies[6] has dealt specifically with obstetric patients in whom the risk of difficult intubation is reported to be eight times greater than in the general surgical population[9]. One of the preoperative tests which should be undertaken by the anaesthetist is an assessment of head and neck mobility. In a recent large study in an obstetric population, Rocke and colleagues used the presence or absence of a short neck as a subjective indication of a likely reduction in atlanto–occipital extension[6]. More recently, Savva found that measurement of sternomental distance, a possible objective indicator of head and neck mobility, was the best of five preoperative tests[8]. Savva found that neither forward protrusion of the mandible nor interincisor gap were useful tests and also suggested that the modified Mallampati test and thyromental distance were neither sensitive nor specific enough for routine use, thus suggesting that sternomental distance should be used as the sole routine test. We were of the opinion however that it was most unlikely that a single test could be used. Nevertheless, and because few obstetric patients were included in the study of Savva, we decided to assess the value of sternomental distance as a sole predictor of difficult laryngoscopy in an obstetric population.

Patients and methods

Sternomental distance and subsequent direct laryngoscopy were recorded in a group of patients presenting for Caesarean section to the obstetric unit at Al Corniche Hospital, a regional obstetric, gynaecology and neonatal hospital. All anaesthesia staff participated after explanation of the study and the data collection form. The hospital undertakes approximately 9000 deliveries annually, and efforts were made to obtain data on as many patients as possible, including both emergency and elective cases. The study was conducted over an 8-month period from November 1, 1994 to June 30, 1995. For each patient the following data were recorded: age, weight, height and method of anaesthesia (general, spinal or extradural). In some cases the patient's weight and height were not available because of the emergency nature of admission.

Before anaesthesia, assessment was made of the airway. This included the ability of the patient to open her mouth, assessment of receding mandible or protruding upper teeth, and subjective assessment of

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head and neck extension. While a view of the oropharynx was undertaken the result was not documented as the purpose of the study was to assess sternomental distance as the sole predictor. During the course of the airway assessment, sternomental distance was measured as the straight distance between the upper border of the manubrium sterni and the bony point of the mentum with the head in full extension and the mouth closed. A ruler was used and the distance measured was approximated to the nearest 0.5 cm. Where there were two anaesthetists assigned to the patient, sternomental distance was measured by one while the other performed laryngoscopy and intubation without knowledge of the measurement. Where only one anaesthetist was assigned to the patient, sternomental distance was measured by an operating department assistant trained to measure the distance in the standardized manner; again the intubating anaesthetist was unaware of the measurement.

After preoperative assessment, the anaesthetist was given the freedom to decide, in consultation with the patient, whether or not the patient should receive general or regional anaesthesia. Because of primarily cultural preferences for not being awake during surgery, the majority of patients chose general anaesthesia. Patients were transferred to the operating room while in the left lateral position, and 30 ml of sodium citrate 0.3 mol litre^{-1} were administered orally before transfer to the operating table. All elective cases also received oral ranitidine 150 mg the night before and the morning of surgery. The majority of emergency cases were given either oral ranitidine 150 mg if first admitted to the labour ward or ranitidine 50 mg i.v. if time allowed. After 3 min of preoxygenation, anaesthesia was induced with either thiopentone or etomidate followed by suxamethonium. Cricoid pressure was applied gradually as the patient lost consciousness.

Immediately after rapid-sequence induction, assessment was made of the view at laryngoscopy, as described by Cormack and Lehane[10]. The classification was as follows: grade I=most of the glottis visible; grade II=only the posterior extremity of the glottis visible; grade III=no part of the glottis visible, only the epiglottis; grade IV=not even the epiglottis visible. The best laryngoscopic view was obtained using a curved Macintosh laryngoscopic blade, with all patients anaesthetized, fully paralysed and in the sniffing position. Intubation was attempted either after cessation of fasciculations or if there were no fasciculations, when the anaesthetist considered jaw relaxation to be adequate. Cricoid pressure was maintained until the trachea was intubated, the cuff inflated and correct tube placement verified.

STATISTICAL ANALYSIS

Patient data are presented as mean (SD). Body mass index (BMI) was determined from weight (kg)/height^2 (m). Pearson's correlation coefficient or Student's unpaired t test was used to determine relationships between age, height, weight, BMI and either sternomental distance or laryngoscopic view. For analysis, laryngoscopic grade was grouped as "difficult" (grades III and IV) or "easy" (grades I and II). Student's unpaired t test was used to assess the significance of the difference in sternomental distance between the groups.

Subsequently, discriminant analysis was used to calculate the most accurate sternomental distance cut-off point for discriminating between the difficult and easy laryngoscopic groups. Sensitivity, specificity, positive and negative predictive values were calculated for this cut-off point (see table 1 for definitions). In addition, a receiver operator characteristic (ROC) curve was used to assess the predictive value of various cut-off points in the prediction of laryngoscopic grade. Logistic regression analysis was used to describe the association between laryngoscopic grade and sternomental distance and to predict the likelihood of a grade III or IV laryngoscopic view. Relative risk and 95% confidence intervals were calculated for the probability of grade III or IV specific cut-off points.

Results

During the study period of 8 months, 5520 mothers delivered in the obstetric unit at the hospital. Of these, 646 (11.7%) patients underwent either elective or emergency Caesarean section. Of the patients studied, 33 underwent operative delivery during either spinal or extradural anaesthesia; therefore, the general anaesthesia group comprised 613 patients and of these, data were collected from 523 patients, representing 85.3% of the obstetric surgical case load during the study period. The majority (73%) of these cases were emergencies. Mean age of the patients was 30.4 (range 15–50) yr, mean weight 78.2 (SD 16.05) kg and mean height 156 (6.47) cm. Mean BMI was 31.95 (5.73). There was no association between sternomental distance and age, weight, height or BMI

Table 1 Definitions of statistical terms

Sensitivity (true-positive fraction)	=	Number of difficult intubations correctly predicted Number of difficult intubations
Specificity	=	Number of easy intubations correctly predicted Number of easy intubations
False-positive fraction	=	1 − specificity
Positive predictive value	=	Number of difficult intubations correctly predicted Number of intubations predicted \to\be difficult
Negative predictive value	=	Number of easy intubations corrected predicted Number of intubations predicted \to \be easy

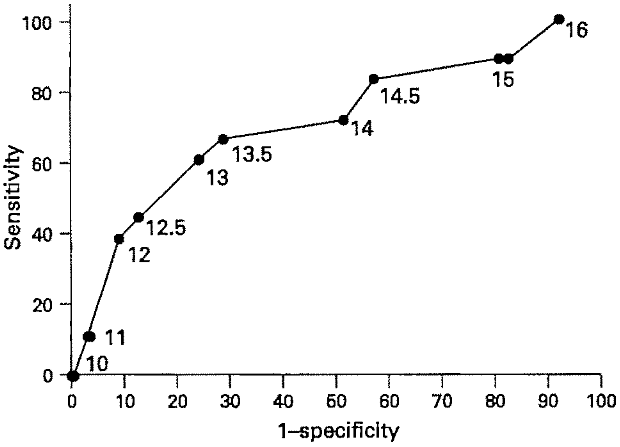

Figure 1 Receiver operating curve (sensitivity *vs* 1− specificity) to assess the predictive value of the various cut-off points in the prediction of laryngoscopic grades III and IV. Sternomental distances are shown and a distance of 13.5 cm proved to be the best cut-off point.

(Pearson's correlation coefficient, $r<0.3$). There was, however, a significant association between age and weight and difficult laryngoscopy (table 2). Patients who had a reduced laryngoscopic view were older and heavier. There were no significant differences in age, weight, height or BMI between the group of patients undergoing general anaesthesia and the group undergoing Caesarean section under regional anaesthesia. No patient had regional anaesthesia solely because of an assessment by the anaesthetist that tracheal intubation would be extremely difficult.

Mean sternomental distance was 14.28 (SD 1.50) cm (range 9–20 cm). Using discriminant analysis, a sternomental distance of 13.5 cm or less was calculated as the most accurate cut-off point for discriminating between difficult (grades III and IV) and easy laryngoscopy (grades I and II). There was a significant difference (P=0.0013) between mean sternomental distance for laryngoscopy grades I and II (14.3 (1.49) cm) and laryngoscopy grades III and IV (13.17 (1.54) cm). Sensitivity, specificity, positive and negative predictive values for the cut-off point of 13.5 cm and for each measured sternomental distance are shown in table 3. Figure 1 shows the ROC curve for the various sternomental distances. Figure 2 shows the relative risks and 95% confidence intervals for the probability of a grade III or IV laryngoscopy compared with grade I or II at specific cut-off points. For example, at a sternomental distance of 12 cm, experiencing a grade III or IV laryngoscopy was 5.6 times (95% CI 2–14) more likely than a

Table 2 Association between "view at laryngoscopy" (grades I and II and grades III and IV combined) and age, weight, and body mass index (BMI) (mean (SD))

	Laryngoscopic view grades I and II		Laryngoscopic view grades III and IV		
	n		*n*		*P*
Age (yr)	496	30.27 (6.45)	18	34.11 (6.11)	0.0132
Weight (kg)	487	77.84 (15.81)	18	87.03 (20.18)	0.0169
Height (cm)	482	155.98 (6 51)	16	156.16 (5.30)	ns
BMI	478	31.88 (5.75)	16	34.22 (4.64)	ns

Table 3 Sensitivity, specificity, positive and negative predictive values for different sternomental distances (cm). (n = Number of patients at each measured sternomental distance. Cases with a sternomental distance > 16.0 cm (n = 40) are not shown)

Sternomental distance (cm)	*n*	Sensitivity	Specificity	Positive predictive value	Negative predictive value
<10.0	2	0	99.6	0	96.6
<10.5	1	0	99.4	0	96.5
<11.0	14	11.1	97.0	11.7	96.8
<11.5	3	11.1	96.4	10.0	96.8
<12.0	33	38.9	90.9	13.2	97.7
<12.5	20	44.4	87.3	11.1	97.8
<13.0	61	61.1	75.6	8.2	98.2
<13.5	24	66.7	71.1	7.6	98.4
<14.0	115	72.2	48.5	4.8	98.0
<14.5	30	83.3	42.9	4.9	98.6
<15.0	120	88.9	19.4	3.8	98.0
<15.5	10	88.9	17.4	3.7	97.8
<16.0	50	100	7.9	3.7	100

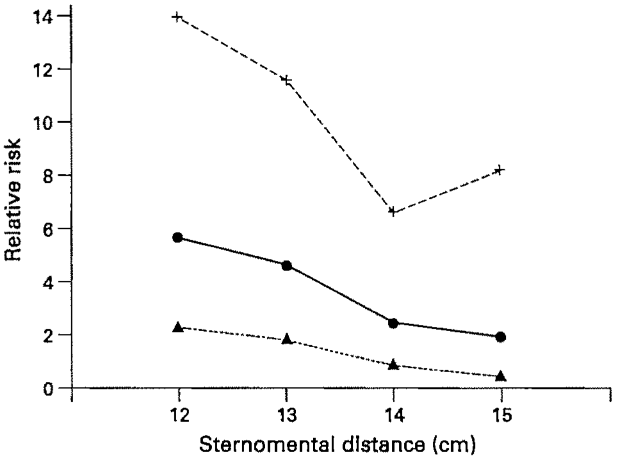

Figure 2 Relative risk (95% CI) of experiencing a grade III or IV laryngoscopy compared with a grade I or II view at laryngoscopy for different sternomental distances.

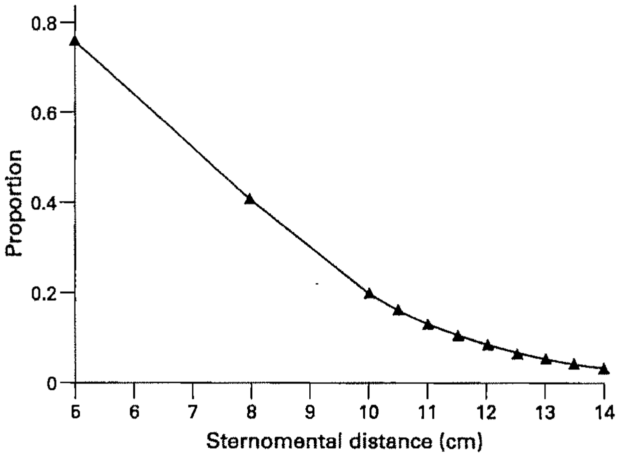

Figure 3 Probability of finding a grade III or IV view at laryngoscopy for each sternomental distance calculated when the prevalence of such grades is 3.5%. Where the prevalence is found to be different, a new probability curve can be calculated using the logistic regression equation logit(P)=−3.738+0.5143×D, where D=sternomental distance and P=probability of grade III or IV laryngoscopy.

grade I or II. Figure 3 shows the probability of experiencing a grade III or IV laryngoscopy for each sternomental distance.

Eighteen (3.5%) of the 523 patients had a grade III or IV view at laryngoscopy. Seventeen of the 18 patients had a grade III while one had a grade IV. Of the 17 who had a grade III view at laryngoscopy, the trachea in 13 was intubated without difficulty with or without the aid of a gum elastic bougie. Of the remaining four, two had the tube passed blindly without the use of a gum elastic bougie while in the other two a laryngeal mask was used because of the difficulty in passing the tracheal tube, even with the aid of a gum elastic bougie. In the grade IV patient, the tube went into the oesophagus after a blinded attempt at intubation. On recognition of oesophageal placement the tube was removed immediately. A laryngeal mask was then inserted but difficulty was experienced with ventilation. The patient was awakened and Caesarean section subsequently completed under spinal anaesthesia.

Discussion

Head extension is thought to be an important factor in determining the ease or difficulty of tracheal intubation[11]. However, several previous studies have made only subjective clinical assessments of reduced atlanto-occipital extension[3 6]. In the study of Bellhouse and Doré the anaesthetist viewed the patient from the side and estimated whether and to what extent there was any reduction in atlanto-occipital extension[3]. In the obstetric study of Rocke and colleagues, no objective assessment was made of reduced neck extension[6], rather, subjective assessment was made on whether or not the patient had a short neck. It was then assumed that the finding of a short neck would be associated with reduced ability to extend the head on the atlanto-occipital joint and thus impede adequate view of the larynx. The presence of a short neck was not only found in nearly 15% of cases but was highly significantly associated with subsequent difficulty at tracheal intubation.

The predictive value of a short neck is somewhat controversial[3]. Bellhouse and Doré questioned the relationship between length of the upper neck and difficult intubation. In their study comparing an easy with a difficult intubation group, those with a longer neck were associated with greater difficulty. Yet paradoxically, within the difficult group the difficulty grade increased as the upper neck became shorter. They concluded that upper neck length, measured radiographically as the length of the four upper cervical vertebrae, should be regarded at best as controversial. Regardless, radiographic methods will always be impractical for routine screening and assessments of short neck remain subjective.

What is required is a quick, simple test of head and neck mobility. Most recently Savva, in a largely non-obstetric population, found sternomental distance to be the most sensitive (82.4%) and specific (88.6%) determinant of difficult intubation of a group of five tests which included a modified Mallampati test, thyromental distance, forward protrusion of the mandible and interincisor gap[8]. A sternomental distance of 12.5 cm or less was found to be the best predictor whereas in this study a distance of 13.5 cm provided the best balance between sensitivity and specificity. Reducing the sternomental distance cut-off point to 12.5 cm or less would result in greater specificity (87.3% *vs* 71.1%), a marginal improvement in the positive predictive value (11.1% *vs* 7.6%) but a significant reduction in sensitivity (44.4% *vs* 66.7%). In clinical practice this implies that by reducing the cut-off point to the same as Savva's criterion, a greater number of difficult laryngoscopies would be missed. The question arises as to which cut-off point from the two studies is the most appropriate. This can only be answered by future epidemiological studies on outcome where a defined test (e.g. sternomental distance at a specified distance) or series of tests are used and with outcome as either difficult laryngoscopy, intubation, or both.

In the study of Savva, four of 350 patients had laryngoscopy grades III or IV (1.14%) which is lower than the 3.5% prevalence in our study. Savva did not state how many of the four were obstetric patients and it is possible that increased weight gain associated with pregnancy resulted in a reduced ability to see the larynx[12]. This would be supported by our finding of an association between reduced laryngoscopic view and weight.

Comment should also be made on the one grade IV laryngoscopy case. Cormack and Lehane suggested that most of these cases would be associated with obvious anatomical pathology which would be easily recognized before operation[10]. Our grade IV case had no obvious pathology either before operation or at the postoperative examination. One possibility is that the laryngoscope blade was inserted too far thus completely obscuring the epiglottis and larynx. This may have been an explanation if the anaesthetist had been inexperienced but this was not the case. The most likely explanation is that the belief that all grade IV cases will have obvious pathology is erroneous.

There are several limitations to this study. First, we did not measure objectively other factors which could have contributed to the reduced laryngoscopic view. As stated, and because of the work of Savva showing sternomental distance to be the best predictor, we set out to determine if this could be reproduced in an obstetric population. A second criticism of the study is that we did not measure whether or not intubation was difficult. However, none of the grade I and II laryngoscopic views had a trachea which was difficult to intubate and most of the 16 grade III and IV cases were managed with ease with the aid of a bougie. Third, several different residents and faculties undertook laryngoscopy and it is possible that a uniform intubation position was not achieved. However, all staff participating in the study had a minimum of 2 yr experience of working solely in this obstetric hospital dealing with a case load where the primary method of provision of anaesthesia for Caesarean section is general anaesthesia. Some studies[13] have standardized the sniffing position by stabilizing the head in a commercial head and neck mould, but we felt that this would have been inappropriate for the obstetric patient.

It is clear that no simple test can be used alone. Measurement of sternomental distance will fail to predict some difficult laryngoscopies and also predict difficult laryngoscopy in a significant number of patients who have a trachea which is easy to intubate. This is not unexpected because on its own sternomental distance fails to take into account relative tongue and pharyngeal size, location of the larynx (mandibular space), overriding maxilla, enlarged incisors, decreased temporal–mandibular joint mobility and a narrow high arched palate. Nevertheless the results of this study confirm, albeit with a reduced predictability than Savva, that sternomental distance can be correlated with laryngoscopic view. We do not believe however that sternomental distance alone can be used as a predictive test, but our results suggest that such a measurement should be included as part of a series of preoperative airway examination tests which should also include view of the oropharynx and thyromental distance.

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References

1. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1988–1990. London: Her Majesty's Stationery Office, 1994.
2. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL. A clinical sign to predict difficult tracheal intubation: a prospective study. *Canadian Anaesthetists Society Journal* 1985; **32**: 429–434.
3. Bellhouse CP, Doré C. Criteria for estimating likelihood of difficulty of endotracheal intubation with the Macintosh laryngoscope. *Anaesthesia and Intensive Care* 1988; **16**: 329–337.
4. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; **61**: 211–216.
5. Freck CM. Predicting difficult intubation. *Anaesthesia* 1991; **46**: 1005–1008.
6. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. *Anesthesiology* 1992; **77**: 67–73.
7. Butler PJ, Dhara SS. Prediction of difficult laryngoscopy: An assessment of the thyromental distance and Mallampati predictive tests. *Anaesthesia and Intensive Care* 1992; **20**: 139–142.
8. Savva D. Prediction of difficult tracheal intubation. *British Journal of Anaesthesia* 1994; **73**: 149–153.
9. Lyons G. Failed intubation: six years' experience in a teaching maternity unit. *Anaesthesia* 1985; **40**: 759–762.
10. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
11. Nichol HC, Zuck D. Difficult laryngoscopy—the 'anterior' larynx and the atlanto-occipital gap. *British Journal of Anaesthesia* 1983; **55**: 141–143.
12. Pilkington S, Carli F, Dakin MJ, Romney M, De Witt KA, Doré CJ, Cormack RS. Increase in Mallampati score during pregnancy. *British Journal of Anaesthesia* 1995; **74**: 638–642.
13. Lewis M, Keramati S, Benumof JL, Berry CC. What is the best way to determine oropharyngeal classification and mandibular space length to predict difficult laryngoscopy? *Anesthesiology* 1994; **81**: 69–75.

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Respiratory mechanics after abdominal surgery measured with continuous analysis of pressure, flow and volume signals†

A. F. NIMMO AND G. B. DRUMMOND

Summary

We studied 10 patients during the first night after upper abdominal surgery to assess the effect of airway obstruction on chest wall mechanics, by recording nasal gas flow and carbon dioxide concentration, rib cage and abdominal dimensions, abdominal muscle activity, and oesophageal and gastric pressures. The mean duration of study of each subject was 5.8 h , and 5.2 h were analysed. The median proportion of time spent breathing with normal mechanics was 29% (interquartile values 0–57%). Abnormal abdominal mechanical events were common and associated with airway obstruction (P<0.001). Two common patterns of abnormal pressure and movement were found. In the first, abdominal pressure decreased at the onset of inspiration and there was a phase lag in abdominal movement. The incidence was 33 (14–50) %. In the second pattern, abdominal pressure decreased and in addition the abdominal wall moved inwards at the onset of inspiration. This occurred for 34 (0–52)% of the time. Both patterns were associated with evidence of increased activation of the abdominal muscles during expiration, changing the relationship of abdominal and pleural pressure changes and chest wall movements. Such changes have been interpreted previously as evidence of diaphragm dysfunction. (*Br. J. Anaesth.* 1996;**77**:317–326)

Key words

Airway, obstruction. Analgesia, postoperative. Complications, respiratory. Surgery, abdominal. Muscle respiratory.

Abdominal surgery influences respiratory pattern, but effects on respiratory muscles are not well described. Measurements of respiratory movements and pressures have led some workers to conclude that the activity of the diaphragm is impaired[1 2]. After surgery, i.v. or extradural administration of opioids can cause episodic airway obstruction and result in periods of hypoxaemia[3 4].

We investigated systematically how analgesia, airway obstruction and hypoxia may be related. To select simple but appropriate methods of measurement of these events, we examined a limited number of patients on the first night after operation. We intend in subsequent studies to measure fewer variables, which could be performed more easily, yet still be interpreted correctly. We also examined the possibility of "diaphragmatic inhibition", which has been inferred in previous studies from the relationship between pleural and abdominal pressure changes.

Patients and methods

THEORY OF ANALYSIS

We used a graphical analysis of respiratory pressures and dimensions. Chest wall movement (fig. 1D) is considered to be in two compartments, rib cage and abdomen, which can move independently to change chest wall and lung volumes, although commonly both expand simultaneously on inspiration and return along the same trajectory on expiration. Action of other muscles, such as the abdominal wall muscles, can separate the inspiratory and expiratory lines. A small amount of asynchrony is normal[5]. Paradoxical motion can occur, despite inspiratory flow, when one compartment moves inward but not sufficiently to negate the outward motion of the other. With no flow, movement is constrained to the "isovolume" line, where the volume changes of the rib cage and abdomen are equal and opposite. Often, outward motion of the abdomen on inspiration is considered to indicate the action of the diaphragm, and outward rib cage motion to indicate the action of the intercostal and other inspiratory rib cage muscles. However, the diaphragm contributes considerably to rib cage expansion. Its costal fibres elevate the rib margin[6]. If the abdominal wall is firm, then the relatively incompressible abdominal contents form a "fulcrum" that allows contraction of the diaphragm to increase abdominal pressure, which expands the lower rib cage through the "zone of apposition" where the diaphragmatic and rib cage pleural surfaces are in contact[7]. The relative amount of rib cage and abdominal displacement caused by diaphragm action depends on the relative compliances of these two compartments[8], and also on the action of other muscle groups at the same time[9]. If the abdominal wall is tense, then the diaphragm mainly expands the rib cage. Observing the motion of the rib cage and abdomen (such as RC/AB ratio) is

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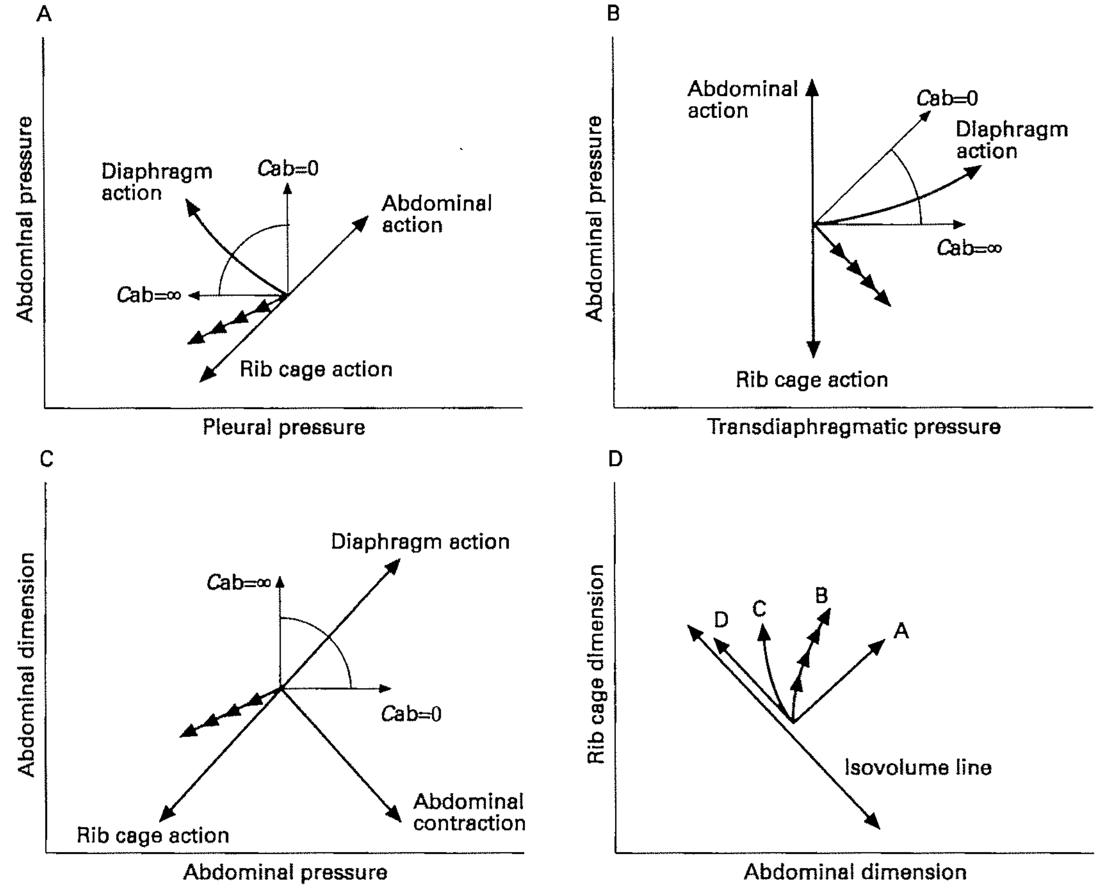

Figure 1 Rib cage and abdominal pressures and dimensions. A: Abdominal *vs* pleural pressure. Normal active inspiration is associated with a decrease in pleural pressure; when the diaphragm contracts, abdominal pressure increases. The direction of the plot depends on the relative compliances of the rib cage and abdomen, and the activities of other muscles, but the direction associated with diaphragm action alone is constrained between the theoretical lines shown for infinite and zero abdominal compliances. Inspiration with the rib cage muscles alone is in the direction "rib cage action" and expiration with the abdominal muscles in the opposite direction (abdominal action). B: Abdominal *vs* transdiaphragmatic pressure (*P*di = *P*ga−*P*pl). C: Abdominal dimension *vs* abdominal pressure. The direction of movement associated with the sole action of rib cage inspiratory muscles, abdominal expiratory muscles and the diaphragm are shown. The direction of the latter depends on abdominal compliance but is constrained within the sector shown. D: Rib cage *vs* abdominal dimensions (arbitrary units). Different trajectories of inspiration are shown: A=normal inspiration; B=inspiration when the abdomen is relatively tense, and most of the motion occurs by the rib cage; C=inspiration with paradoxical inward motion of the abdomen; and D=an isovolume manoeuvre where the increase in rib cage volume is the same as the decrease in abdominal volume. In each quadrant, the line with multiple arrowheads indicates the direction of movement during inspiration where there is predominant contribution from rib cage muscles.

not enough to allow changes in activity of the diaphragm to be inferred unless the compliances of the two compartments remain constant.

ANALYSIS OF PRESSURES

Measurements of abdominal and pleural pressures (conveniently plotted graphically in fig. 1) allow better discrimination of respiratory muscle action.

Action of the rib cage muscles

Inspiratory action of rib cage muscles (such as external intercostals and scalenes) expands the rib cage and decreases pleural pressure *P*pl. If the diaphragm is inactive, transdiaphragmatic pressure is zero (*P*di=*P*ab − *P*pl). Consequently, as pleural pressure decreases, abdominal pressure decreases equally. The diaphragm and abdominal contents are drawn cranially, and the abdominal wall moves inwards.

Abdominal expiratory muscle action

Expiratory muscle action alone has the opposite effect on *P*ab and *P*pl. Inward motion of the abdominal wall increases abdominal pressure, displaces the diaphragm cranially, increases pleural pressure and causes expiration. Inspiration can then occur if the abdominal muscles subsequently relax and result in descent of the diaphragm. This action is difficult to distinguish from rib cage activation.

Diaphragm action

Contraction of the diaphragm generates a transdiaphragmatic pressure. The relative changes in pleural pressure and abdominal pressure during inspiration depend on the relative compliances of the rib cage and abdomen (fig. 1A). If the compliance of the abdomen were infinite, then pressure change would occur only by a decrease in pleural pressure. In practice, transdiaphragmatic pressure cannot be generated without a corresponding increase in abdominal pressure. If the abdominal compartment has a very small compliance, abdominal pressure increases with a very small reduction in pleural pressure. It follows that the trajectory of the *P*ab against *P*pl plot caused by the diaphragm acting alone lies between these lines. If the diaphragm and rib cage muscles act together in inspiration, they can move the pressures in the segment between the line indicating zero abdominal compliance and the line indicating rib cage muscle action alone.

Diaphragm action may also be assessed with a plot of abdominal pressure *vs* transdiaphragmatic pressure (fig. 1B). Rib cage action decreases abdominal pressure with no change in *P*di and results in a vertically descending plot. Abdominal expiratory muscle action increases abdominal pressure with no change in *P*di (generating a plot opposite to that seen with rib cage inspiratory action, as has been noted in the *P*ab *vs P*pl diagram). Action of the diaphragm against a rigid abdomen results in equal increases in *P*ab and *P*di. If abdominal compliance is infinite, *P*di increases alone. Hence this plot differs from the previous (*P*ab *vs P*pl plot) because the sector for sole action of the diaphragm is smaller. However, as in the preceding diagram, any combination of diaphragm and rib cage action generates a plot in the sector between the line of zero abdominal compliance and the rib cage line. Although more information on the activity of chest wall muscles may be obtained from such plots than from measurements of compartmental movement, the relative contribution of each group of muscles cannot be distinguished exactly by this analysis: in particular, abdominal relaxation and rib cage activity appear similar.

ABDOMINAL DIMENSION/ABDOMINAL PRESSURE PLOT (FIG. 1C)

Action of inspiratory rib cage muscles and relaxation of abdominal muscles can be distinguished by plotting abdominal dimension *vs* abdominal pressure, as in a compliance graph. *Contraction of the expiratory muscles* generates inward movement of the abdominal wall and an increase in abdominal pressure. Inward wall movement can occur only if another part of the abdominal container is displaced, such as by cranial displacement of the diaphragm. If both the diaphragm and abdominal expiratory muscles contract at the same time, abdominal pressure increases with little decrease in abdominal dimension. *Inspiratory action of the rib cage muscles alone* moves the abdominal wall inwards and decreases abdominal pressure. *Diaphragm action* increases abdominal pressure and displaces the abdominal wall outward, and the slope of this plot indicates the compliance of the abdominal wall. Simultaneous inspection of this plot and the *P*ab *vs P*pl plot (fig. 1A) allows inspiratory events associated with abdominal relaxation to be distinguished from those caused by the inspiratory action of the rib cage.

AIRWAY OBSTRUCTION

If airway resistance is increased, muscle shortening is reduced and the tension developed by the muscles for a given degree of activation is increased. Pleural pressure decreases more, and gastric pressure increases less, as there is less displacement of the diaphragm. In addition, pleural pressure can no longer be used as an appropriate indicator of lung volume, as lower airway, alveolar and pleural pressures all decrease substantially during the inspiratory effort. In this condition, transpulmonary pressure (*P*ao − *P*pl, where *P*ao=pressure at the airway opening) differs considerably from the pressure difference between the alveolus and pleural space which is proportional to lung volume.

We developed the hypothesis that prevention of muscle shortening could increase neural activation by reflex mechanisms, notably the stretch reflex mediated by muscle spindles. Rib cage muscles have a clear postural role and are richly supplied with muscle spindles[10]. Impedance of inspiration may result in their reflex activation, and an increased contribution to inspiratory force. This will alter the trajectories of the *P*ab *vs P*pl, *P*ab *vs P*di and abdominal volume *vs* pressure plots in the directions shown in figure 1.

PROCEDURE

After obtaining approval from the regional Ethics Committee and written informed consent, we studied patients aged 40 yr or more, undergoing major abdominal surgery that would involve an incision at least partly above the umbilicus, and who would be cared for after operation in the surgical high dependency unit. Exclusion criteria were severe cardiac, respiratory or renal disease, or a body weight more than 130% of that predicted on the basis of sex, age and height. For postoperative analgesia, six patients received patient-controlled analgesia (PCA) with either morphine or diamorphine i.v., and four received a continuous thoracic extradural infusion of 0.125% bupivacaine containing diamorphine 0.033 mg ml^{-1} at 10 ml h^{-1}.

A nasogastric tube with an integral oesophageal balloon (Mallinkrodt) was modified by attaching a gastric balloon to the tube tip. This was inserted via a nostril during anaesthesia, and placed to allow estimation of oesophageal and gastric pressures (*P*oes and *P*ga) using differential transducers (Furness FC10). *P*oes and *P*ga are used as measures of *P*pl and *P*ab, respectively. Transdiaphragmatic pressure (*P*di) was calculated as (*P*ga − *P*oes). The gas volume in each balloon was checked regularly and adjusted. Pressure calibration was against a water manometer.

Patients received oxygen 2 litre min^{-1} via nasal cannulae after operation. Pressure fluctuations in the nasal cannulae were measured to allow estimation of gas flow at the nose[11]. A narrow sampling tube was inserted through the centre of one cannula to allow sampling of carbon dioxide concentration for measurement by an infrared capnometer (Engstrom Eliza). Rib cage and abdominal dimensions were measured by inductance bands placed around the rib cage immediately below the axillae and around the abdomen at the level of the umbilicus, and avoiding the rib margins if possible. Disposable ECG electrodes were attached in the right upper quadrant of the abdomen to measure abdominal muscle EMG[12]. An Ohmeda 3700 pulse oximeter with a finger probe was used to record oxygenation continuously. The signals were recorded using a high speed analogue to digital converter (RTM8, Digitimer Ltd) which played into a domestic video recorder and allowed up to 8 h of continuous recording, sampling at a rate of 11 kHz per channel. The monitoring apparatus was set up in the evening after operation, and recordings made over the first night. One investigator (A.F.N.) remained with the patient overnight, supervising the quality of the recorded signals. Occasional adjustments were necessary, particularly to the gastric and oesophageal balloons, and the nasal flow measurement system.

Further analysis involved playing back the videotaped record onto an eight-channel chart recorder (Graphtec WR3600). These records were then analysed by an observer who was unaware of the clinical circumstance of the patient. Each record was divided into segments of 5 min each, and each segment was classified according to preset criteria. First, the segment was classified as analysable, depending on the satisfactory recording of all the signals. Next, the presence or absence of central apnoea or hypopnoea, or obstructive apnoea or hypopnoea, was determined for each analysable segment. Central apnoea was determined by the absence of nasal flow, no changes in oesophageal pressure and no change in rib cage or abdomen dimension for more than 15 s. Central hypopnoea was defined by a reduction in amplitude of gas flow at the nose with a reduction in oesophageal pressure change. Obstructive hypopnoea was defined by a decrease in gas flow at the nose, associated with an increase in oesophageal pressure changes, and obstructive apnoea as no gas flow and increased oesophageal pressure changes.

The records were then re-analysed for the presence of mouth breathing, which was defined as continued chest wall movements, no change in oesophageal pressure swings and loss of nasal flow and carbon dioxide signals. This definition implies that the patient was breathing through the mouth and not through the nose: however at other times the patient may have been breathing through both the nose and mouth.

Finally, each segment was inspected for the presence of abnormalities of chest wall mechanics which were classified according to table 1. An inspiratory attempt was recognized from a decrease in oesophageal pressure. Because the exact time of *onset* of inspiration on the pressure trace was often indistinct because of cardiac oscillations, the times of *onset and end of inspiration* were obtained from the tracing of rib cage dimension. In one patient whose rib cage dimension sometimes decreased on inspiration, oesophageal pressure was used to time inspiration. EMG signals were not analysed formally by integration but were used to assess the presence and pattern of abdominal muscle activity.

Statistical analysis of the association between abnormalities present in each time segment of each subject was performed using a log-linear model with the P4F program from the BMDP package (BMDP statistical software, 1988). Partial association was sought between pairs of the following categorical variables, after allowing for interaction between the other two variables: airway patency (i.e. airway clear or airway obstructed); chest wall mechanics (i.e. normal or abnormal chest wall and pressure changes); route of respiration (i.e. nose or mouth breathing); subject number (i.e. each patient).

Table 1 Summary of changes at the start of inspiration for different breathing patterns

	Change in gastric pressure	Movement of abdomen	Movement of rib cage
Normal	Increase	Outward	Outward
Gastric pressure paradox	Decrease	Outward	Outward
Abdominal movement paradox	Decrease	Inward	Outward
Ric cage paradox	Increase	Outward	Inward

To investigate the patterns of changes in the recorded variables, values for each patient were re-digitized from the replayed analogue signals using a commercial software package (Cardas, version 2.07, Oxcams Ltd, Oxford) at 20 Hz and plotted at 10 Hz using Fig P for windows version 1 (Biosoft, Cambridge), with a standard plot as in figures 3–5.

Results

Patient details are shown in table 2. Most patients were aged more than 60 yr and none was overweight. Results are given as median (quartile values). The number of 5-min periods of recording for each patient was 71 (68–72) and of these, 7 (5–10) could not be analysed. There was no evidence of airway obstruction in only 10 (3–22) of the periods analysed, and no abnormality of chest wall mechanics in 14 (0–36). Mouth breathing varied considerably between patients, being present in a median of 10 (1–38) periods per patient. The frequency of these abnormalities for each patient is given in table 3. There was no clear difference between patients using PCA and those receiving extradural analgesia. Airway obstruction and abnormal chest wall mechanics were related significantly ($P<0.0001$), but the relationship between mouth breathing and abnormal mechanics was not significant ($0.05<P<0.1$).

Table 3 also gives the relative distribution of the abnormalities of chest wall mechanics. There was no clear difference between the two types of analgesia. Both gastric pressure paradox and abdominal movement paradox were frequent (33 (14–50) % and 34 (0–52) % of the time, respectively). We noted that when these patterns were present, there was increased abdominal muscle activity on the EMG record. Ventilatory frequency over the study varied considerably between patients, with a median of 13.5 (9.5, 14.5) bpm. For each patient, ventilatory frequency also varied considerably within the study, increasing with arousal. There were no episodes of central apnoea. Determination of the incidence of central hypopnoea was difficult. We defined central hypopnoea as a reduction in both nasal gas flow and oesophageal pressure change during inspiration, that is a decrease in both tidal volume and effort. However, such changes were universal during recovery from an episode of airway obstruction, associated with a presumable decline in hypercapnic stimulation. A decrease in both nasal gas flow and oesophageal pressure change was not evident at other times, and we concluded that "central hypopnoea" was not present in these patients.

PATTERN OF CHANGE IN PRESSURE AND MOTION

Most breathing was either normal, had paradox of gastric pressure or had paradox of both gastric pressure and abdominal movement. An example is given in figure 2, showing progression from a normal pattern, to paradox of gastric pressure, then abdomi-

Table 2 Details of patients. RUQ = Right upper quadrant of the abdomen. Opioid doses are given as milligrams of morphine, assuming half the potency of diamorphine. Intraoperative doses include those given on recovery from anaesthesia. All extradural opioids were diamorphine. Intraoperative doses given to patients with extradurals are divided into extradural (e) and i.v. Pre-study amount = Amount given before the study started.

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	Incision	Analgesia	Opioid administration Intraoperative	 Pre-study	 During study
1	M	46	185	81	RUQ	PCA	15	28	8
2	M	64	175	74	Transverse	Extradural	13 i.v.	8	3
3	F	65	165	65	Transverse	PCA	10	20	9
4	M	74	173	60	Midline	PCA	10	7	4
5	F	71	153	67	RUQ	Extradural	3 e	8	4
6	M	43	173	82	Midline	PCA	12	40	13
7	M	64	168	83	Transverse	Extradural	2 e	7	4
8	M	64	163	81	Midline	PCA	10	19	6
9	F	73	157	67	RUQ	PCA	10	26	4
10	M	66	171	74	Transverse	Extradural	5 i.v.+3 e	5	4

Table 3 Incidence and duration of respiratory abnormality in the patients studied

		Incidence of abnormality (%)			Percentage of time spent with different mechnical patterns			
Patient No.	Analgesic method	Abnormal mechanics	Airway obstruction	Mouth breathing	Normal	Gastric pressure paradox	Abdominal motion paradox	Rib cage motion paradox
1	PCA	97	69	58	2	56	42	0
2	Extradural	56	42	2	44	8	48	0
3	PCA	46	89	18	54	45	0	0
4	PCA	35	90	14	65	24	5	6
5	Extradural	100	100	91	0	43	57	0
6	PCA	100	98	69	0	9	91	0
7	Extradural	18	0	0	82	18	0	0
8	PCA	89	78	0	11	89	0	0
9	PCA	100	94	54	0	50	50	0
10	Extradural	67	72	8	33	16	51	0

nal movement paradox, followed by resumption of normal breathing.

Representative plots of breaths of each type, obtained from the records of another patient, from a period of 30 min, are shown in figures 3–5.

Normal breath (fig. 3)

Plots of *P*ga *vs P*oes and *P*ga *vs P*di showed "looping". At the start of inspiration, *P*oes decreased promptly. The direction of the early inspiratory plot was only just in the "diaphragm action" sector. In the second part of the inspiration, gastric pressure increased and remained increased during the first part of expiration. The plot of abdominal dimension against gastric pressure showed that in the first half of inspiration there was little increase in either gastric pressure or abdominal volume. In the second half of inspiration, abdominal dimension increased smoothly as gastric pressure increased. The plot of rib cage and abdominal dimensions showed that early in inspiration the relative proportion of rib cage dimension increase was greater than that of the abdomen, whereas during expiration both dimensions decreased progressively and in the same proportion, so clockwise "looping" is seen. This pattern was seen in all patients.

The changes in this type of breathing can be summarized as oesophageal pressure and rib cage dimension changing in advance of abdominal dimension, with gastric pressure and abdominal dimension changing in phase in the later part of inspiration. In expiration, gastric pressure and transdiaphragmatic pressure decreased, and oesophageal pressure increased. The plot of abdominal dimension against gastric pressure decreased along a plot that was the reverse of inspiration.

Gastric pressure paradox (fig. 4)

Figure 4 shows a breath sampled in the same patient, approximately 30 s before the example in figure 3. Gastric pressure decreased early in inspiration. All patients showed this pattern of change at some time during the study. The *P*ga *vs P*oes and *P*ga *vs P*di plots showed an initial downward descent, and then an increase in gastric pressure in the second part of inspiration. The abdominal dimension/gastric pressure plot showed a deflection in a horizontal direction (i.e. no change in abdominal dimension during early inspiration) before both dimensions increased in the second half of inspiration. This pattern of abdominal dimension/*P*ga plot was most common, but in two patients an increase in abdominal dimension occurred as gastric pressure decreased. On the dimension plot, outward rib cage motion started with no initial change in abdominal dimension. In the second half of inspiration, and in expiration, the shape of this plot remained similar to that seen in a normal breath.

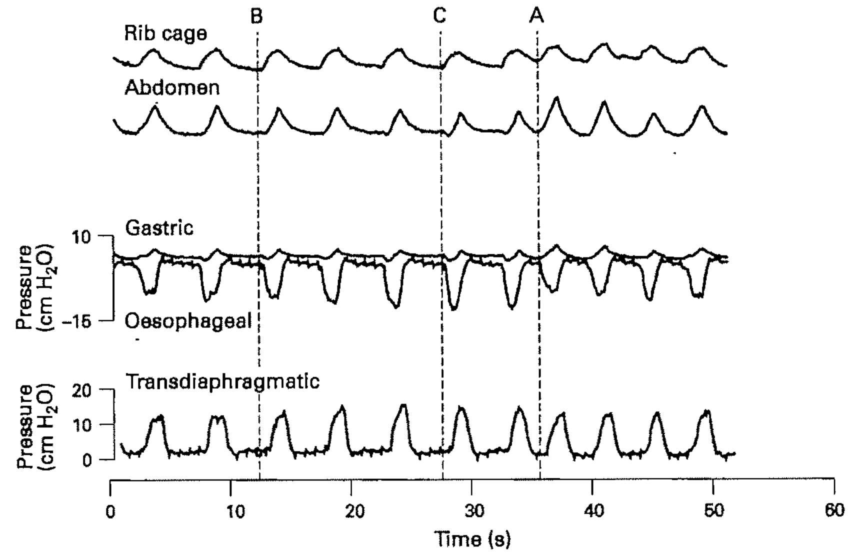

Figure 2 Chest wall dimensions, oesophageal and gastric pressures, and derived diaphragmatic pressure in one patient, illustrating the different types of abnormality. At A, a normal breath with increases in rib cage and abdominal dimension, and gastric pressure, at the start of inspiration; at B, gastric pressure decreases at the onset of inspiration; at C, both gastric pressure and abdominal dimension decrease at the start of inspiration.

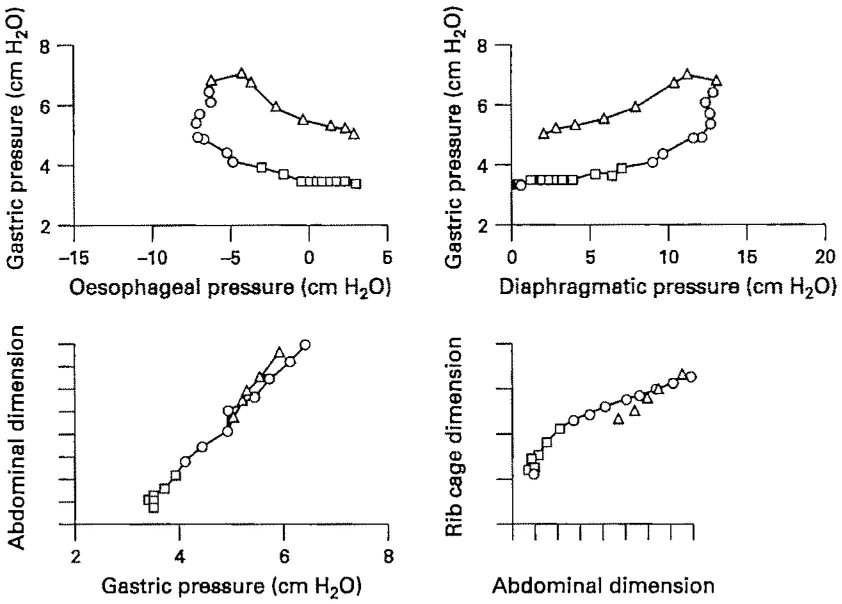

Figure 3 A single breath showing a normal pattern of breathing. The first half of inspiration is shown with the symbols (□) the second half with the symbols (○) and the subsequent early part of expiration with the symbol (△). Rib cage and abdominal dimensions are in arbitrary units; abdominal dimension is used with a common scale on the two plots. (The final part of expiration has been omitted for clarity, see text for further discussion.)

Abdominal movement paradox (fig. 5)

Gastric pressure, oesophageal pressure and abdominal dimension decreased during the first part of inspiration. On the plot of abdominal dimension and gastric pressure, gastric pressure and abdominal dimension decreased in concert at the start of inspiration but then increased in the second half of inspiration. A particular feature of this type of breathing was that during expiration, abdominal dimension decreased as gastric pressure either remained unchanged or increased. This is shown clearly in the example, and was seen in all subjects. As expected, rib cage dimension increased but abdominal dimension decreased at the start of inspiration, but again in late inspiration both dimensions increased together.

In several subjects, rapid and frequent changes between these breathing patterns were noted, whereas in other patients more stable patterns of breathing, particularly that of gastric pressure paradox, were noted. Often airway obstruction became progressively more severe and ended with apparent arousal and restoration of a temporarily normal breathing pattern.

All patients received oxygen 2 litre min^{-1} from a nasal cannula. Despite airway obstruction, oxygen saturation did not decrease to less than 90% in any patient. Occasionally the oxygen saturation display was less than 90%, but in each of these events, the observer could see both the patient and the plethysmographic waveform displayed by the oximeter, and judged the low saturation value artefactual, usually caused by patient movement.

Discussion

We have described the patterns of respiratory mechanics that occur after major abdominal surgery

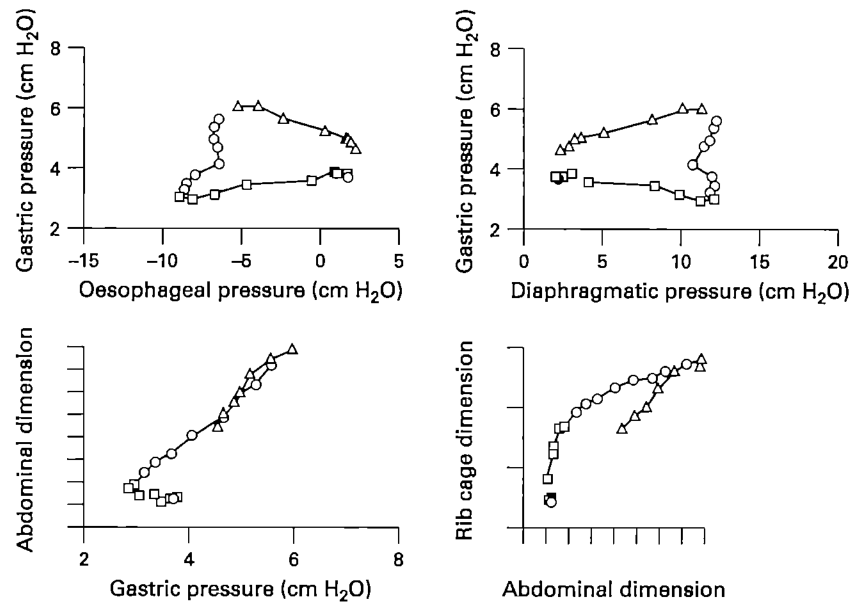

Figure 4 A single breath, from the same patient as in figure 4, showing a reduction in gastric pressure at the onset of inspiration. Symbols as in figure 3. Rib cage and abdominal dimensions are in arbitrary units. Note the increased "looping" in the gastric pressure *vs* oesophageal pressure and gastric pressure *vs* diaphragmatic pressure plots during the first part of inspiration, indicating a phase shift, with pressure in the oesophagus "leading" gastric pressure.

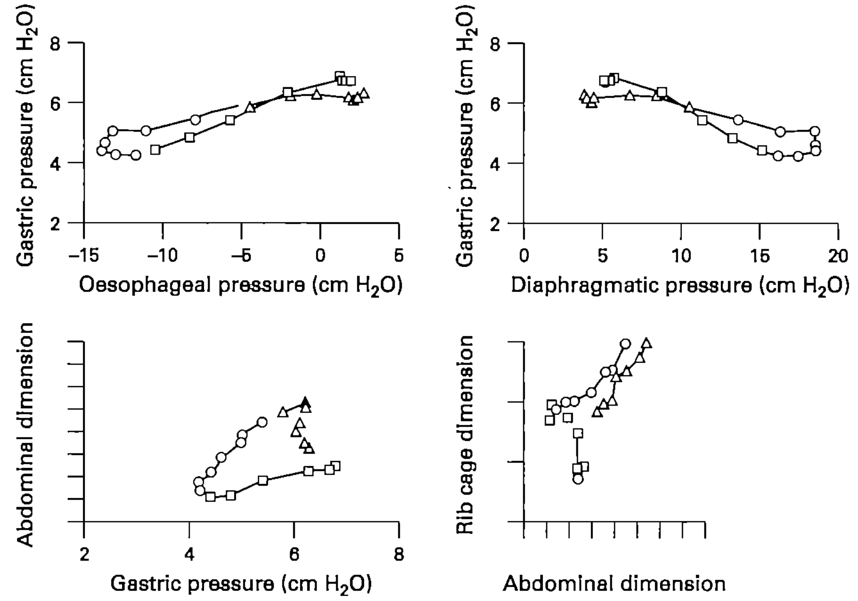

Figure 5 An example of a single breath, from the same patient as in figure 4, showing a reduction in abdominal dimension at the onset of inspiration. Symbols as in figure 3. Rib cage and abdominal dimensions are in arbitrary units. Note the greater changes in oesophageal and transdiaphragmatic pressure. These changes suggest increased tension in the inspiratory muscles. The decrease in gastric pressure at the onset of inspiratory attempt, synchronous with the decrease in abdominal dimension, indicates an increased contribution from rib cage muscles.

in association with breathing and breathing disturbances. These patterns proved remarkably consistent, although the relative changes were complex. Statistical analysis of the changes was categorical because several factors prevented a more quantitative approach.

The oesophageal balloon method is not of great value for estimating the absolute value of pleural pressures in supine subjects, particularly when lung volume is small, although pressure changes can be measured satisfactorily[13]. In our subjects, abdominal muscle activity was frequently present to some degree, so the absolute values of gastric pressure would be affected. However, we believe that within-breath changes can be used descriptively, as we have done in the example shown, and that breaths a few minutes apart (as in figs 3–5) can be compared usefully.

Measurement of chest wall motion using inductance bands is a simple and non-invasive method, but is often difficult in recumbent patients[14 15] or after operation[16]. Our patients were always supervised closely to ensure that the bands remained in about the same place, but changes in position disturbed the signal for some time and was the most common reason for an uninterpretable trace. There are several alternative methods for calibration of the inductance band device, but only the original isovolume manoeuvre is sufficiently robust statistically to properly partition abdominal and rib cage volume contributions[17]. Repeated calibration of the bands under the conditions of this study was impossible, and we only used these signals qualitatively. For example, a simultaneous reduction in the changes in oesophageal pressure and rib cage dimension was interpreted as a decrease in respiratory drive. Such changes were noted cyclically in some patients during recovery from an episode of obstruction.

We used nasal pressure signals similarly to provide a breath-by-breath indication of flow. Clear changes were seen in association with obstruction, followed by arousal, with transient increases in flow and breathing movements. EMG signals can be quantified by rectification and integration, but we were unsure of the stability of the recording system over several hours. The signals were used to indicate the phase and pattern of external oblique activity.

The patterns of motion observed are worthy of comment, and each variable studied will be considered in turn. Pressures related to elastic and resistance components can be distinguished by their relationship to flow and volume change. For example, the flow-related component of the oesophageal pressure change is more than doubled after sedation with midazolam[18] because airway resistance is increased. Oesophageal pressure change is greater, for the same degree of neural activation of the inspiratory muscles, if inspiration is impeded. This is partly because the muscles shorten less and more pressure is generated. The extreme example of this is occluded inspiration where the muscles contract but cannot shorten, other than to distort the chest wall, and oesophageal pressure decreases considerably more than during a normal breath. If airway resistance is increased, but flow is *not* reduced, then the inspiratory muscle activity must have increased. Transpulmonary pressure during inspiration, associated with that flow, is greater because of the increased resistance. We infer that airway obstruction is responsible for the increased change in oesophageal pressure early in inspiration that could be seen when the abdominal wall moved *inward* during inspiration, and this inference was supported by the statistical association between episodes of airway obstruction and abnormal chest wall mechanics.

In a normal breath, gastric pressure and abdominal dimension increase and decrease together, suggesting that abdominal motion is the result of diaphragm action, and that the compliance of the anterior abdominal wall does not change during the respiratory cycle.

On the other hand, abdominal wall compliance clearly *does* alter when gastric pressure decreases at the start of inspiration (fig. 4). At the same time, rib cage dimension increases and oesophageal pressure decreases rapidly. Such changes could be caused by the inspiratory action of the rib cage. They could equally well be the result of relaxation of the abdominal muscles, if these muscles have acted to decrease the dimensions of the lower rib cage, or possibly caused by both of these actions. These alternatives can be distinguished partly by considering the abdominal dimension/gastric pressure plot, so that the inspiratory action of rib cage muscles and relaxation of the abdominal expiratory muscles generate movement of the plotted values in different directions. The slope of the plot depends on the compliance of the abdomen. Abdominal compliance is small if the abdominal muscles and diaphragm are contracting at the same time, whereas it is greater if the inspiratory rib cage muscles are active alone, as the abdominal contents are drawn passively in a cranial direction as pleural pressure is reduced. In this study, abdominal pressure decreased with little change in abdominal dimension, so the abdomen or diaphragm was relaxing. Previous observations suggest that large changes in gastric pressure, particularly during expiration, can be related directly to abdominal muscle activity[19 20].

When both gastric pressure and abdominal volume decrease together, there must be a dominant effect of the rib cage inspiratory muscles. Even when the abdomen moves paradoxically on inspiration, transdiaphragmatic pressure still increases (fig. 5), indicating that the diaphragm is active, and that it is contracting against an increased respiratory impedance. Indeed, pressure changes tended to be greater when respiration was impeded. However, this action does not displace the abdominal contents because gastric pressure shows no increase. In such conditions, assessment of "dysfunction" using changes in transdiaphragmatic and gastric pressure is impossible. We had no index of diaphragmatic activation, as could be provided by electromyography. However, the commonly used index of contractility, the ratio of EMG to *P*di, is altered by both posture and the degree of abdominal muscle activity[21], and therefore this would not have been of great value. Other workers have found that maximum diaphragmatic electromyographic activity is reduced after abdominal surgery but this appears to be in proportion to the reduction in tidal volume[22]. Contractility appears unaffected[23]. Similarly, extradural analgesia was noted to restore both electrical activity and tidal volume by approximately similar amounts[24]. Paradoxical chest wall movements similar to those we have described have been noted in obese patients with sleep apnoea[25] and patients with airway obstruction after surgery[26].

We suggest that these abnormal patterns of gastric pressure and abdominal dimension indicate activity of the inspiratory rib cage muscles and abdominal expiratory muscles. Airway resistance probably activates the intercostal muscles because of the stretch reflex. Intercostal muscles have many muscle spindles[10] and have a clear reflex response to imposed loads[27 28]. In contrast, the diaphragm has few spindles and no clearly defined reflex response to loads, other than via vagal reflexes[29]. Rib cage movement is thus greater in early inspiration and this feature can be seen to a lesser extent even in "normal breathing" after operation (fig. 3). The decrease in gastric pressure was similar but not identical to that seen in unilateral diaphragm paralysis[30] or in the horse[31] when the abdominal muscles are used to assist expiration. EMG assessment of the relative timing and activation of the diaphragm and intercostal muscle activity would be helpful to examine the possible reflex augmentation of intercostal activity in early inspiration.

Previous workers have used the relationship between gastric and oesophageal pressure changes to assess the relative contribution of the diaphragm[1 2]. This approach is generally valid if *only* the diaphragm or inspiratory rib cage muscles, or both, are active; in the present situation, there may be differences in the *timing* of activity of these muscles, the magnitude of their reflex activation by increased airway resistance may differ and, in addition, the abdominal muscles are active in expiration.

Opioid administration may enhance rib cage stiffness. Patients in this study received only moderate quantities of opioid (table 2). Extradural analgesia had no clear influence on abnormal chest wall mechanics.

Opioid administration may also influence the observed changes by provoking airway obstruction, particularly during sleep. Previous observers found that episodes of airway obstruction were associated with episodes of desaturation. Catley and colleagues[3] found that hypoxaemic episodes occurred during sleep and were associated with obstructive apnoea and opioid analgesia. However, their identification of episodes of airway obstruction depended entirely on the quantitative use of the inductance band method, which is unlikely to remain accurate for long periods of time. Although these workers have illustrated paradoxical changes in chest wall dimensions similar to those in this study[26], such movements have been incompletely investigated and described. We found that outward rib cage motion was almost completely preserved during airway obstruction and conclude that although this movement does not indicate abnormalities of breathing in patients after operation, it provides a reliable indication of inspiratory effort. Measurement of gas flow at the nose in addition to rib cage movement allows airway obstruction to be recognized. The combined measurement of rib cage movement and gas flow at the nose could provide an indication of airway obstruction with minimal disturbance to the patient. An episode of obstruction would be recognized reliably by outward movement of the rib cage (showing an inspiratory effort) with absence of gas flow at the nose.

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References

1. Ford GT, Whitelaw WA, Rosenal TW, Cruse PJ, Guenter CA. Diaphragm function after upper abdominal surgery in humans. *American Review of Respiratory Disease* 1983; **127**: 431–436.
2. Simonneau G, Vivien A, Sartene R, Kunstlinger F, Samii K, Noviant Y, Duroux P. Diaphragm dysfunction induced by upper abdominal surgery–role of postoperative pain. *American Review of Respiratory Disease* 1983; **128**: 899–903.
3. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
4. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled analgesia. *British Journal of Anaesthesia* 1990; **64**: 267–275.
5. Sharp JT, Goldberg NB, Druz WS, Danon J. Relative contributions of rib cage and abdomen to breathing in normal subjects. *Journal of Applied Physiology* 1975; **39**: 608–618.
6. Loring SH, Mead J. Action of the diaphragm on the rib cage inferred from a forcebalance analysis. *Journal of Applied Physiology* 1982; **53**: 756–760.
7. Urmey WF, De Troyer A, Kelly KB, Loring SH. Pleural pressure increases during inspiration in the zone of apposition of diaphragm to ribcage. *Journal of Applied Physiology* 1988; **65**: 2207–2212.
8. Macklem PT, Gross D, Grassino A, Roussos C. Partitioning of inspiratory pressure swings between diaphragm and intercostal/accessory muscles. *Journal of Applied Physiology* 1978; **44**: 200–208.
9. Estenne M, Yernault JC, De Troyer A. Ribcage and diaphragm abdomen compliance in humans. Effects of age and posture. *Journal of Applied Physiology* 1985; **59**: 1842–1848.
10. Duron B, Jung-Caillol MC, Marlot D. Myelinated nerve fibre supply and muscle spindles in the respiratory muscles of cat: quantitative study. *Anatomy and Embryology* 1978; **152**: 171–192.
11. Guyatt AR, Parker SP, Mcbride MJ. Measurement of human nasal ventilation using an oxygen cannula as a pitot-tube. *American Review of Respiratory Disease* 1982; **126**: 434–438.
12. Duggan J, Drummond GB. Activity of lower intercostal and abdominal muscle after upper abdominal surgery. *Anesthesia and Analgesia* 1987; **66**: 852–855.
13. Drummond GB, Wright ADG. Inaccuracy of oesophageal pressure for pleural pressure estimation in supine anaesthetised subjects. *British Journal of Anaesthesia* 1983; **55**: 585–593.
14. Whyte KF, Gugger M, Gould GA, Molloy J, Wraith PK, Douglas NJ. Accuracy of respiratory inductive plethysmograph in measuring tidal volume during sleep. *Journal of Applied Physiology* 1991; **71**: 1866–1871.
15. Spier S, England S. The respiratory inductive plethysmograph: bands versus jerkins. *American Review of Respiratory Disease* 1983; **127**: 784–785.
16. Fratacci MD, Kimball WR, Wain JC, Kacmarek RM, Polaner DM, Zapol WM. Diaphragmatic shortening after thoracic surgery in humans—effects of mechanical ventilation and thoracic epidural-anesthesia. *Anesthesiology* 1993; **79**: 654–665.
17. Zimmerman PV, Connellan SJ, Middleton HC, Tabona MV, Goldman MD, Pride NB. Postural changes in ribcage and abdominal volume–motion coefficients and their effect on calibration of a respiratory inductance plethysmograph. *American Review of Respiratory Disease* 1983; **127**: 209–214.
18. Montravers P, Dureuil B, Molliex S, Desmonts JM. Effects of intravenous midazolam on the work of breathing. *Anesthesia and Analgesia* 1994; **79**: 558–562.
19. Duggan JE, Drummond GB. Abdominal muscle activity and intraabdominal pressure after upper abdominal surgery. *Anesthesia and Analgesia* 1989; **69**: 598–603.
20. Gilmartin J J, Ninane V, de Troyer A. Abdominal muscle use during breathing in the anesthetized dog. *Respiration Physiology* 1987;**70**:159–171.
21. Lopata M, O'Connor TD, Onal E. Effects of position on respiratory muscle function during CO$_2$ rebreathing. *Respiration* 1985; **47**: 98–106.
22. Pansard J-L, Mankikian B, Bertrand M, Kieffer E, Clergue F, Viars P. Effects of thoracic extradural block on diaphragmatic electrical activity and contractilty after upper abdominal surgery. *Anesthesiology* 1993; **78**: 63–71.
23. Dureuil B, Viires N, Cantineau J-P, Aubier M, Desmonts J-M. Diaphragmatic contractility after upper abdominal surgery. *Journal of Applied Physiology* 1986; **61**: 1775–1780.
24. Mankikian B, Cantineau JP, Bertrand M, Kieffer E, Sartene R, Viars P. Improvement of diaphragmatic function by a thoracic extradural block after upper abdominal surgery. *Anesthesiology* 1988; **68**: 379–386.
25. Staats BA, Bonekat HW, Harris CD, Offord KP. Chest wall motion in sleep apnea. *American Review of Respiratory Disease* 1984; **130**: 59–63.
26. Catley DM. Postoperative analgesia and respiratory control. In: Jones JG, ed. *Effects of Anesthesia and Surgery on Pulmonary Mechanisms and Gas Exchange. International Anesthesiology Clinics, vol. 22 No 4.* Boston: Little, Brown and Company, 1984; 95–111.
27. Altose MD, Stanley NN, Cherniak NS, Fishman AP. Effects of mechanical loading and hypercapnia on inspiratory muscle EMG. *Journal of Applied Physiology* 1975; **38**: 467.

28. Sampson MG, De Troyer A. Role of intercostal muscles in the rib cage distortions produced by inspiratory loads. *Journal of Applied Physiology* 1982; **52**: 517–523.
29. Kobylarz EJ, Daubenspeck JA. Immediate diaphragmatic electromyogram responses to imperceptible mechanical loads in conscious humans. *Journal of Applied Physiology* 1992; **73**: 248–259.
30. Lisboa C, Pare PD, Pertuze J, Contreras G, Moreno R, Guillemi S, Cruz E. Inspiratory muscle function in unilateral diaphragmatic paralysis. *American Review of Respiratory Disease* 1986; **134**: 488–492.
31. Koterba AM, Kosch PC, Beech J, Whitlock T. Breathing strategy of the adult horse (equus caballus) at rest. *Journal of Applied Physiology* 1988; **64**: 337–346.

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Thoracic impedance used for measuring chest wall movement in postoperative patients

G. B. DRUMMOND, A. F. NIMMO AND R. A. ELTON

Summary

Thoracic impedance (TTI) and rib cage inductance band (IB) signals were measured in 10 patients during the first night after abdominal surgery, and compared by successive correlation of the change in each signal. Poor matching of the signals occurred, on average, for 94 min either because of movement or differences in the waveform. There were frequent episodes of transient poor correlation, generally associated with transient respiratory disturbance, predominantly airway obstruction (58%). Thoracic impedance measurements are simpler than inductance band methods for detecting rib cage movement and may be useful for large studies of respiratory abnormalities in patients after operation. (*Br. J. Anaesth.* 1996;**77**:327–332)

Key words

Ventilation, postoperative. Ventilation, rib cage. Measurement techniques, thoracic impedance.

Breathing abnormalities, including episodes of central and obstructive apnoea[1] and disturbed chest wall movements[2], are frequent after major surgery. Central and obstructive apnoea can be distinguished by measures of both chest wall movement and airway flow. We know of no studies of patients after operation in which the reliability of such measurements has been assessed, and only one in which the number of artefacts has been reported[3]. This type of information is particularly important if automated methods of data analysis are contemplated.

Chest wall movement is commonly attributed to contributions from the rib cage and abdomen, and the motion of these two "compartments" can be used to predict respired volume[4]. After operation, abdominal movements are frequently abnormal or even paradoxical[2], whereas rib cage movement remains in phase with respiratory effort and better indicates inspiratory activity. Chest wall movement is measured most often by means of inductance bands[5] which detect changes in the self-inductance of a coil placed round the chest wall in an extensible band: changes in the signal are thought to represent changes in area, although this may not be correct[6]. Circumferential length sensors have also been used[7–9]. Such devices can estimate tidal volume but are affected by body motion[10], posture[11], sleep[12] and airway obstruction[13], and the bands can be inconvenient. We have re-examined the value of transthoracic impedance (TTI) to indicate rib cage movement[14]. The method is simpler and less obtrusive, using adhesive electrodes to measure the voltage generated across the chest surfaces by the presence of a small constant current, usually applied via the sensor electrodes themselves. Previous studies attempted to relate TTI directly to respired volume, but this is now recognized as being inappropriate[15 16]. TTI has been compared previously with inductance bands[17 18] but not in patients after surgery, so the suitability of the two methods for this is not known. We have studied how well TTI and rib cage inductance signals compare, to give a qualitative index of rib cage movement, how reliable these methods are and the reasons for discrepancies between the signals.

Patients and methods

Patients gave informed written consent and local Ethics Committee approval was granted. We studied 10 patients after major abdominal surgery over the first night after operation while they were in a surgical high dependency unit. Criteria for admission to the study were an abdominal incision extending above the umbilicus and age more than 40 yr. Patients were excluded if they were chronically hypercapnic or had a body weight more than 130% of that expected on the basis of sex, age and height. Analgesia was provided with either a thoracic extradural infusion or i.v. patient-controlled injections of morphine.

Transthoracic impedance was measured with a device constructed in the Department of Medical Physics and Medical Engineering. It gave a constant current of 1.5 mA rms, frequency 70 kHz and was connected to the chest wall via two Medicotest ECG electrodes, one on the right mid-axillary line at a level corresponding to the V6 ECG electrode position and the other medial to the top of the left anterior axillary line. Earlier studies showed these positions gave more reliable waveforms than when electrodes were placed in both mid-axillary lines. The amplifier output was filtered (bandwidth 0.01–1.4 Hz, −6 dB octave^{-1}).

Rib cage movement was measured with an inductance band placed round the rib cage immediately below the axillae. It used an alternating current of 100 kHz and self-inductance was measured with another device made by the Department of Medical

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Table 1 Incidence and duration of episodes of poor correlation caused by patient movement and lack of correspondence between the two waveforms

		Patient movement		Poor waveform correspondence (min)		
Patient No	Total time measured (min)	No. of episodes	Total duration of episode (min)	TTI abnormal	Inductance abnormal	Both abnormal
1	358	3	10	0	0	0
2	357	1	3	0	0	0
3	356	2	5	185	0	0
4	358	2	14	58	0	19
5	357	1	2	141	0	13
6	357	4	18	0	114	0
7	356	14	46	33	0	0
8	357	0	0	129	0	0
9	357	2	4	0	0	0
10	353	4	7	0	0	133

Physics and Medical Engineering. The amplifier output was filtered (bandwidth 0.03–16 Hz, −6 dB octave^{-1}). Another band was placed around the abdomen at the level of the umbilicus, but only the signal from the rib cage inductance band was used for comparison with the TTI signal.

Gas flow at the nose was measured from pressure fluctuations in a nasal oxygen cannula system[19] measured using a differential transducer (Furness FC10, Bexhill, Kent). Signals were sampled continuously every 88 μs with an AD converter (PCM8, Medical Systems Corporation, Digitimer, Welwyn Garden City, UK) and recorded on magnetic tape. Each record was replayed onto an eight-channel chart recorder (Graphtec WR3600) at 60 mm min^{-1} to allow inspection of the waveform patterns. Signals were passed also to a second AD converter into respiratory logging software (Cardas version 2.07, Oxcams, Oxford) sampling at 20 Hz. Each patient provided approximately 6 h of recorded data.

The waveforms were compared by taking successive 10-s blocks of data of the TTI and rib cage impedance signals. In each 10 s, samples of each signal were obtained at 5 Hz, giving 50 values. Each value was subtracted from the following one to give the relative changes of each signal which were then correlated by least squares linear regression (SPSS 4.0 for Unix V/386 Intel 80386). The strength of the correlation gave an index of the similarity of the two signal waveforms. These correlation estimates are presented as discrete values in the figures that have expanded time scales. For each patient, the correlation values of each 10-s block were plotted using a time scale of 40 cm h^{-1}. A typical short section of such a plot is shown in figure 1. The general pattern of these values was either a consistent excellent correlation with *r* values greater than 0.8, with occasional transient decreases in the *r* value; or periods of time when the *r* values were variable and consistently less than 0.8. If the *r* value was less than 0.8 for more than 30% in any 5 min this was termed "poor matching" and these periods measured for each patient. The chart records were inspected to determine the reason for the poor correlation, and classified into two categories: patient movement, recognized by a short (1–5 min) episode where all

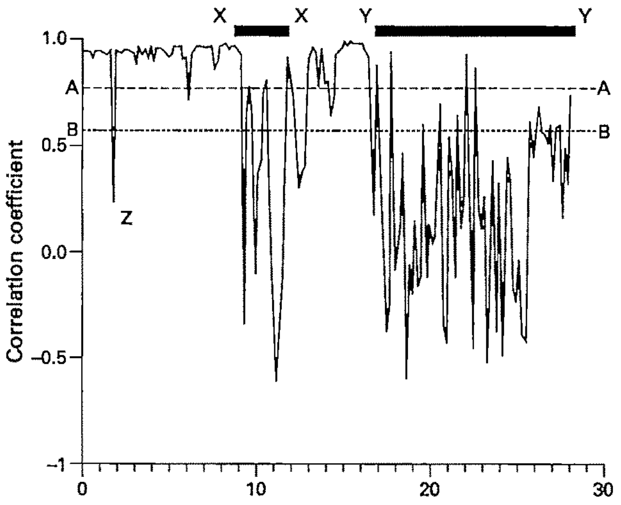

Figure 1 A sample of successive correlation plot illustrating the method of analysis. The horizontal bars (X–X, Y–Y) represent times when the correlation coefficient was less than 0.8 (line A–A) for more than 70% of the time. The first bar (X–X) indicates a period of 3 min caused by movement, and the second (Y–Y) a persistent period of poor matching. At the start of the plot, there was a transient episode of loss of correlation (Z) (r<0.6, line B–B).

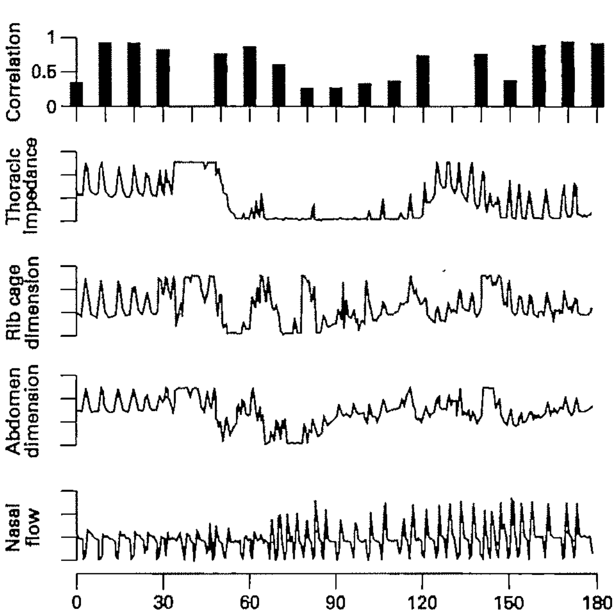

Figure 2 A plot of successive correlation values and the measured variables during a period of patient movement. Note also the poor nasal flow at the start of the trace, before arousal at about 30 s.

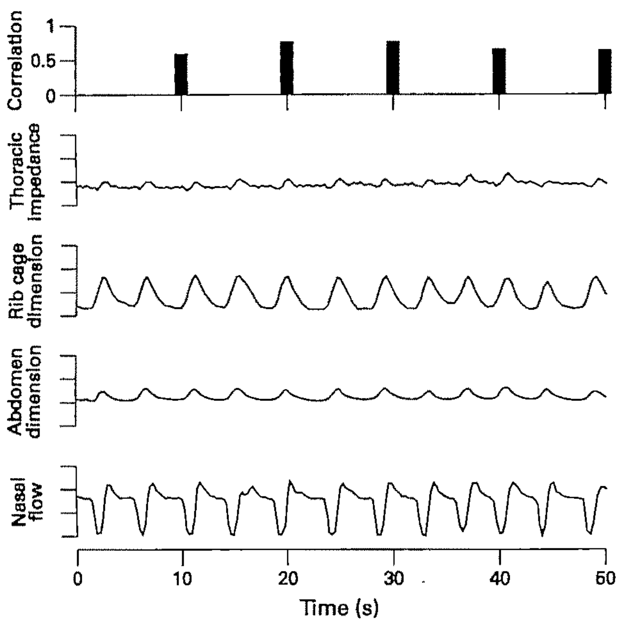

Figure 3 Poor correlation associated with a TTI signal which is biphasic and of low amplitude.

signals became markedly disturbed; or a poor relationship between the TTI and inductance band waveform shapes. In these latter periods, a signal with an unclear and complex waveform was classified as "abnormal" (usually a decrease in amplitude or a biphasic pattern). Results are presented for either one, or both, signals being of this type.

In the rest of the recording, when matching of the signals was generally good, episodes of transient decrease in the *r* value could occur when *r* became less than 0.6, usually for only one or two values. Each of these events was identified, related to the chart recording of the original signals and classified according to the apparent reason for the poor correlation. The respiratory pattern of the patient was inferred from the nasal flow signal leading up to the event, in relation to the rib cage and abdominal inductance signals, and classified as showing: apnoea, normal nasal flow pattern, mild or severe obstruction of nasal flow, or an abnormally large breath (usually after an episode of obstruction). Obstruction to flow was also recognized by a change in the waveform of the nasal flow signal. The TTI and inductance band signals were classified into one of the following categories: absent or low amplitude signal, stable waveform, change in baseline (successive cycles having different amplitude of turning points), large change in signal amplitude, change in waveform or signal waveform that was opposite in phase to the other signals (paradoxical waveform). The relationships between these states for the three signals were investigated by logical analysis using Minitab PC version 8.2 run using DOS 6.2.

Results

We studied 10 patients (five females), mean age 68 yr and weight 89% of expected (range 72–100%). The waveforms were poorly matched for a mean of 94 min (table 1). Motion artefact accounted for 11 min of poor matching. An episode of movement is shown in figure 2. Inadequate waveform matching accounted for the remainder of the time that the signals were poorly matched. The TTI waveform was poor on average for 58 min per patient. Both signals were poor for a mean of 16 min. An episode when the TTI signal was poor is shown in figure 3. TTI amplitude was small and the wave was biphasic in comparison with rib cage and abdomen inductance band signals. Four of 10 subjects were responsible for the majority of the poor TTI signals: 58, 129, 141 and 185 min, respectively.

There was no apparent relationship between the method of analgesia and the inadequate waveform. Periods of poor waveform generally started and

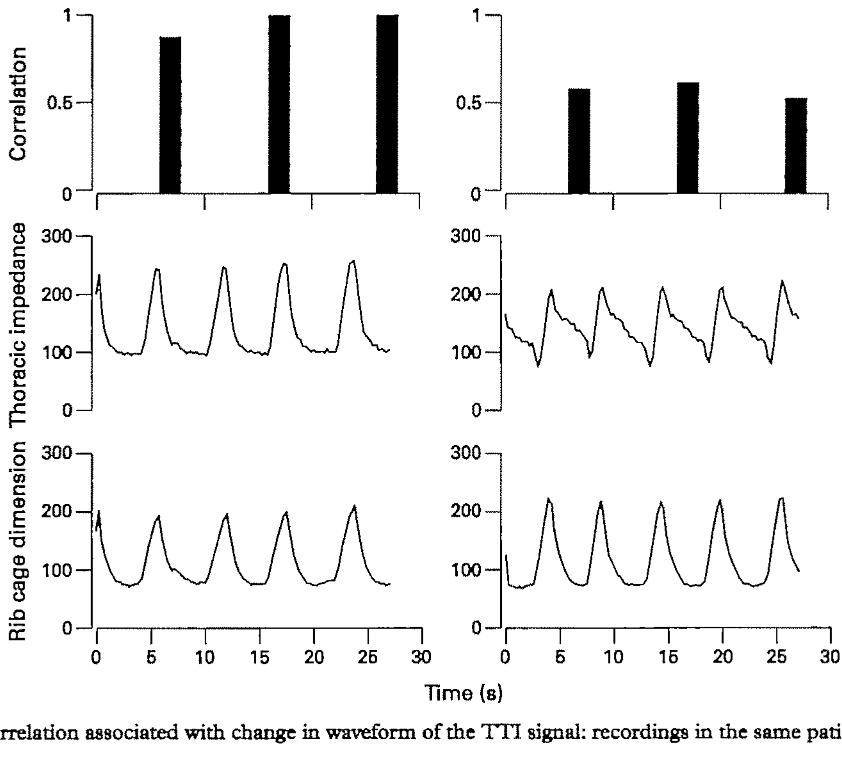

Figure 4 Change in correlation associated with change in waveform of the TTI signal: recordings in the same patient, the second 15 min after the first.

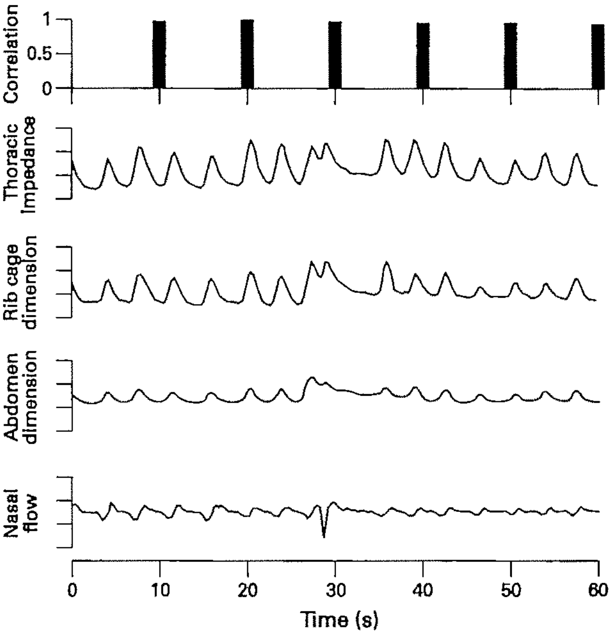

Figure 5 Persistently good correlation despite disturbances in waveform of both TTI and inductance signals.

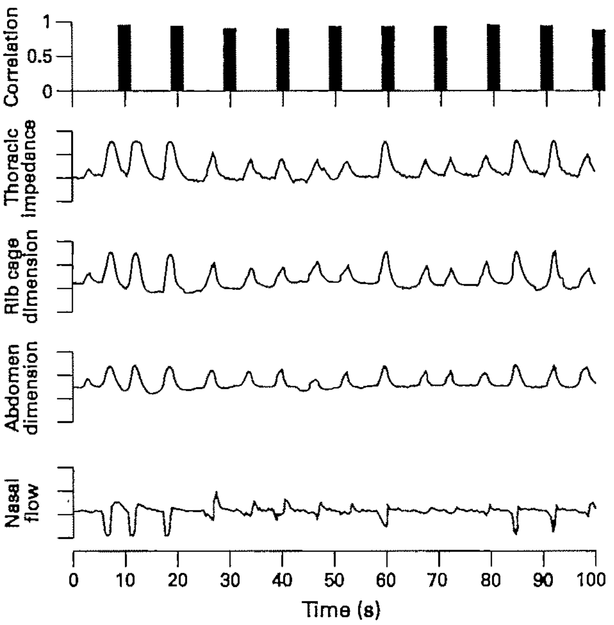

Figure 6 Persistently good correlation despite disturbances in breathing pattern and airway obstruction.

ceased with episodes of movement, probably indicating times when the patient moved into a different position. Figure 4 shows a change in correlation after a period of movement in a patient. The poor matching is associated with a change in the TTI waveform which shows a decrease in thoracic impedance at the onset of inspiratory flow.

If the correlation of waveforms was satisfactory (r >0.8 for >70% of the time), the correspondence between TTI and rib cage inductance band signals was very good, even when there were transient changes in the pattern of respiration (fig. 5) or episodes of airway obstruction (fig 6). Episodes of severe airway obstruction resulted in transient reduction in correlation, either because of changes in waveform (fig. 7) or changes in the signal baseline (fig. 8).

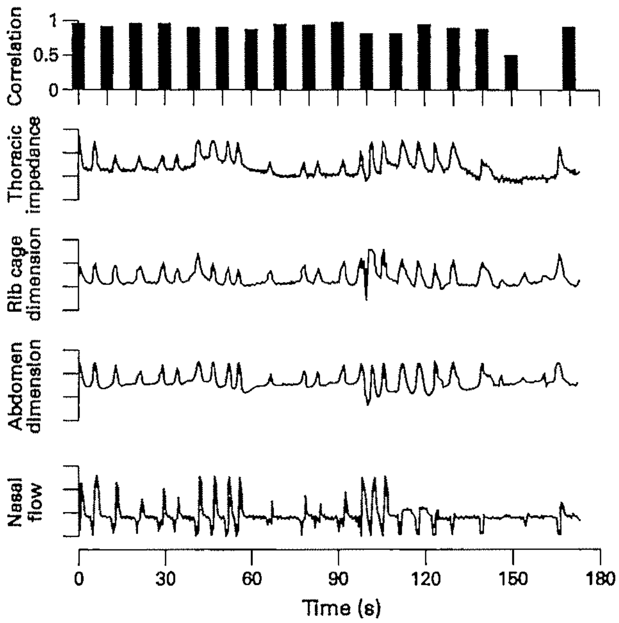

Figure 7 Repeated episodes of airway obstruction resulting in changes in waveform and baseline, and reduced correlation.

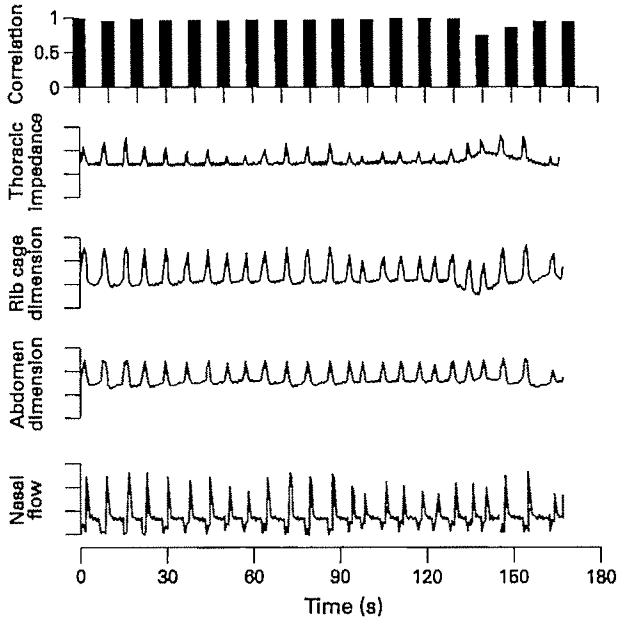

Figure 8 A minor episode of airway obstruction at 90–150 s with disturbances in TTI and inductance baseline and reduced correlation.

There were a total of 390 episodes of transient poor correlation in the 10 patients, with patients showing between 9 and 81 episodes of this type (table 2). More than 50% were associated with airway obstruction. Large breaths after an episode of obstruction accounted for 18% of events. In 17% of transient poor correlation events, there was no abnormality in the nasal flow signal. Baseline position change of the TTI signal most frequently reduced the correlation (45% of episodes), for example with airway obstruction (fig. 8). Changes in waveform of the TTI signal caused 25% of episodes, and in 19% there was no clear fault. Most commonly, the inductance band signal associated with a transient reduction in the correlation did not change (34% of episodes). The baseline changed in 25% of the episodes, the waveform altered in 15% and a small signal was present in 13%.

Absent airway flow and no signal from the TTI trace (which could indicate central apnoea) was noted only once. During inspection of the paper records it was evident that satisfactory correlation values could persist despite minor disturbances in the baselines of the signals, and in the signal waveform and amplitude, such as in figure 8. The traces were not examined systematically for this, as objective criteria for such events would have been difficult to establish.

Discussion

Chest wall impedance has been used to monitor respiration for many years[20]. The early development of the method has been reviewed by Pacela[21]. Realizing that independent movements of rib cage, abdomen and trunk contribute to lung volume changes[10] and that TTI is related to rib cage dimension[22] has tempered the hope that TTI could be related directly to lung volume, although alternative approaches using electrode arrays may provide more information on lung volume[23–25]. Comparisons of TTI with other methods have only been for short periods of time, often for only a few minutes[18]. We set out to use TTI to indicate chest wall movement and thus classify abnormalities of breathing. We have found from studies of oesophageal pressure in such patients that the most frequent respiratory abnormality is obstructive apnoea. In this case, the rib cage inductance band signal remains in phase with respiratory efforts, whereas abdominal movements may cease or become paradoxical[2]. Nasal flow often changed abruptly. In this study we are reasonably confident therefore that the decreases in flow represented obstruction rather than hypopnoea (when the flow waveform was attenuated but of similar shape) or change to mouth breathing (which we found to be almost always only expiratory).

For comparison, we used inductance bands. If the output signal is AC-coupled to remove baseline fluctuations, this method gives a long-term satisfactory qualitative index of movement, being disturbed only when the patient changes position. In this study, the inductance band system was judged to give a poor signal for a single prolonged episode (114 min) in only one subject and in 15% of the isolated events of poor correlation. However, inductance bands and TTI obviously detect different physical characteristics, and some of the discrepancies we found may be caused by other but nevertheless "real" changes, such as intrathoracic fluid shifts, which alter TTI measurements. Visual inspection and previous experience of the relationship between lung volume and chest wall dimension measurements led us to classify the simpler waveforms as "correct" although this is to some extent arbitrary.

Table 2 Incidence of abnormal waveforms associated with transient poor correlation. Values are percentage of total episodes of poor correlation

	TTI	Inductance
Abnormality		
Small wave	3	13
Normal	19	34
Baseline shift	45	25
Abnormal waveform	25	15
Other	8	13

The frequency of breathing was generally approximately 15 (range 7–30) bpm. Consequently, the sample rate of 5 Hz used gave 10–40 samples for each breath, usually 20. More rapid sampling would give small increments between successive values that could be affected by noise in the signals. With 10 s for each correlation, we compared the correspondence of the waveform over approximately two breaths which is probably what is done when comparisons are "by eye", and the number of samples was sufficiently great to ensure a good chance of detecting correlation. We detected three types of loss of correspondence between the signals. The first type, classified as movement artefact, disturbed both signals equally. The second type, poor waveform correspondence, was often judged to be the "fault" of the TTI signal: only on one occasion did the inductance method give a poor signal. Finally, there were frequent events when there was temporary loss of correlation between the signals. However, inspection of these events showed that on most occasions the TTI signal remained "interpretable". The most common reason for poor correlation was a baseline shift. The TTI apparatus we used was intended for measurement of the duration of inspiration and expiration of each breath and had an extended low frequency response for this purpose, and this reduced its capacity to recover from baseline changes. A reduction of the low frequency response of the TTI system would reduce the incidence of these episodes.

In 25% of cases, the baseline shift was associated with an episode of obstruction, and it may be that the shift was caused by changes in blood volume in the chest during obstruction. Another common reason for poor correlation was a change in waveform (99 of 390 events), and an uninterpretable signal was present on only four occasions. The method we used of testing for waveform comparability gives false positives: occasions when the TTI signal, alone, could be useful but the comparability of the waves was poor. The false negative rate, when the correspondence between the signals may have been poor but the correlation method did not indicate this, is probably small. We had no automated method or specific criteria for identifying false negative events, but carefully examined each chart, several times, without finding this possibility.

Studies of respiratory movement are generally for short measurement periods[26–30]. Overnight studies measuring respiratory movement or gas flow are uncommon, the study of Catley and colleagues being an exception[1]. They measured chest wall movements and interpreted paradoxical movements as airway obstruction, but gave no details of how much time satisfactory signals were absent. In another study using a simplified inductance band system, 14 of 63 records were excluded because of inadequate quality, and artefacts occurred at 0.2–0.7 per hour, which is a very low rate compared with this study. These were detected by inspection of the charts only, perhaps a less rigorous test of signal quality[3]. Similar studies by others, using inductance bands[31] or chest wall sensors[32], used computerized methods for analysis but provided no details of the means of validation of the data.

A more recent study[33] involved 20 patients, each studied both before operation and for 60–70 h after operation. An observer was present continuously to exclude artefact, but no details are provided of the proportion of record excluded.

We believe that our study is the first report of the quality of postoperative respiratory monitoring. The quality of these signals was affected by patient factors such as motion and also by technical factors such as electrode contact, position, and the position and stability of the inductance bands. Ideal signals would be obtained from a patient who slept in one position for the whole night: such a patient would certainly be over-sedated and likely to develop pressure sores, atelectasis and sputum retention (at least). Thus loss of signal is inevitable: breathing should not be a completely continuous process. Clinical investigations require differentiation of central and obstructive apnoea and this can be done with an index of the presence or absence of respiratory movements and a nasal flow signal. This study showed that TTI can provide this index, and as TTI measurements are simpler than inductance band methods, larger numbers of patients may be studied more easily.

Acknowledgements

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References

1. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
2. Nimmo AF, Drummond GB. Respiratory mechanics after abdominal surgery measured with continuous analysis of pressure, flow and volume signals. *British Journal of Anaesthesia* 1996; **77**: 317–326.
3. Frater RAS, Moores MA, Parry P, Hanning CD. Analgesia-induced respiratory depression: comparison of meptazinol and morphine in the postperative period. *British Journal of Anaesthesia* 1989; **63**: 260–265.
4. Mead J, Peterson N, Grimby G. Pulmonary ventilation measured from body surface movements. *Science* 1967; **156**: 1383–1384.
5. Sackner JD, Nixon AJ, Davis B, Atkins N, Sackner MA. Non-invasive measurement of ventilation during exercise using a respiratory inductive plethysmograph. *American Review of Respiratory Disease* 1980; **122**: 867–871.
6. Martinot-Lagarde P, Sartene R, Mathieu M, Durand G. What does inductance plethysmography really measure? *Journal of Applied Physiology* 1988; **64**: 1749–1756.
7. Ogilvie RD, Houghton IT. A simple respiration monitor. *Electroencephalography and Clinical Neurophysiology* 1982; **54**: 347.
8. Morel DR, Forster A, Suter PM. Noninvasive ventilatory monitoring with bellows pneumographs in supine subjects. *Journal of Applied Physiology* 1983; **55**: 598–605.
9. Brimacombe J, MacFie A, Masters A. The extensometer—use in spontaneously ventilating awake volunteers. *Anaesthesia* 1992; **47**: 872–877.
10. Smith JC, Mead J. Three degrees of freedom description of movement of the human chest wall. *Journal of Applied Physiology* 1986; **60**: 928–934.
11. Zimmerman PV, Connellan SJ, Middleton HC, Tabona MV, Goldman MD, Pride NB. Postural changes in ribcage and abdominal volume–motion coefficients and their effect on calibration of a respiratory inductance plethysmograph. *American Review of Respiratory Disease* 1983; **127**: 209–214.
12. Whyte KF, Gugger M, Gould GA, Molloy J, Wraith PK, Douglas NJ. Accuracy of respiratory inductive plethysmograph in measuring tidal volume during sleep. *Journal of Applied Physiology* 1991; **71**: 1866–1871.
13. Tobin MJ, Guenther SM, Perez W, Mador MJ. Accuracy of the respiratory inductive plethysmograph during loaded breathing. *Journal of Applied Physiology* 1987; **62**: 497–505.
14. Geddes LA, Hoff HE, Hickman DM, Moore AG. The impedance pneumograph. *Aerospace Medicine* 1962; **33**: 28–33.
15. Hoffman S, Vedekin R, Atlas D. Respiratory monitoring with a new impedance plethysmograph. *Anaesthesia* 1986; **41**: 1139–1142.
16. Ashutosh K, Gilbert R, Auchincloss JH, Erlebacher J, Peppi D. Impedance pneumograph and magnetometer methods for monitoring tidal volume. *Journal of Applied Physiology* 1974; **37**: 964–966.
17. Brouillette RT, Morrow AS, Weese-Mayer DE, Hunt CE. Comparison of respiratory inductance plethysmography and thoracic impedance for apnea monitoring. *Journal of Pediatrics* 1987; **111**: 377–383.
18. Ross Russell RI, Helms PJ. Evaluation of three different techniques used to measure chest wall movements in children. *European Respiratory Journal* 1994; **7**: 2073–2076.
19. Guyatt AR, Parker SP, Mcbride MJ. Measurement of human nasal ventilation using an oxygen cannula as a pilot-tube. *American Review of Respiratory Disease* 1982; **126**: 434–438.
20. Schaefer H. Ein einfaches gerat zur registierung der atmung und anderer mechanischer vorgange. *Pflugers Archiv (Berlin)* 1944; **247**: 606–610.
21. von Euler C. The functional organisation of the respiratory phase-switching mechanisms. *Federation Proceedings* 1977; **36**: 2375–2380.
22. Gamboa R, Adair BN. Thorax resistivity in children and adults. *Journal of Applied Physiology* 1967; **23**: 109–113.
23. Cooley WL, Longini RL. A new design for an impedance pneumograph. *Journal of Applied Physiology* 1968; **25**: 429–432.
24. Severinghaus JW, Catron C, Noble W. A focused electrode bridge for unilateral lung resistance. *Journal of Applied Physiology* 1974; **32**: 526–530.
25. Henderson RP, Webster JG. An impedance camera for spatially specific measurements of the thorax. *IEEE Transactions on Biomedical Engineering* 1978; **25**: 250–254.
26. Gilbert R, Auchincloss JH, Peppi D. Relationship of rib cage and abdomen motion to diaphragm function during quiet breathing. *Chest* 1981; **80**: 607–612.
27. Ford GT, Whitelaw WA, Rosenal TW, Cruse PJ, Guenter CA. Diaphragm function after upper abdominal surgery in humans. *American Review of Respiratory Disease* 1983; **127**: 431–436.
28. Simonneau G, Vivien A, Sartene R, Kunstlinger F, Samii K, Moviant Y, Duroux P. Diaphragm dysfunction induced by upper abdominal surgery–role of postoperative pain. *American Review of Respiratory Disease* 1983; **128**: 899–903.
29. Duggan JE, Drummond GB. Abdominal muscle activity and intraabdominal pressure after upper abdominal surgery. *Anesthesia and Analgesia* 1989; **69**: 598–603.
30. Pansard J-L, Mankikian B, Bertrand M, Kieffer E, Clergue F, Viars P. Effects of thoracic extradural block on diaphragmatic electrical activity and contractilty after upper abdominal surgery. *Anesthesiology* 1993; **78**: 63–71.
31. Etches RC, Sandler AN, Lawson SL. A comparison of the analgesia and respiratory effects of extradural nalbuphine or morphine in postthoracotomy patients. *Anesthesiology* 1991; **75**: 9–14.
32. Clyburn PA, Rosen M, Vickers MD. Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block. *British Journal of Anaesthesia* 1990; **64**: 446–449.
33. Nozaki Taguchi N, Oka T, Kochi T, Taguchi N, Mizuguchi T. Apnoea and oximetric desaturation in patients receiving extradural morphine after gastrectomy: A comparison of intermittent bolus and patient controlled administration. *Anaesthesia and Intensive Care* 1993; **21**: 292–297.

British Journal of Anaesthesia 1996;77:333–334

Preoxygenation in children using expired oxygraphy

P. J. Butler, H. M. Munro and M. B. Kenny

Summary

We performed preoxygenation on 25 patients, aged 1–12 yr. End-tidal oxygen sampling was used to find the duration of preoxygenation required to reach an end-tidal oxygen fraction of 0.9. All children reached this end-point within 80 s, which was markedly more rapid than that observed in adult subjects. The clinical applications of this form of monitoring in children are discussed. (*Br. J. Anaesth.* 1996;**77**:333–334)

Key words

Anaesthetic techniques, preoxygenation. Anaesthesia, paediatric. Children. Monitoring, oxygen.

Preoxygenation of the lungs is an important component of rapid sequence induction of anaesthesia and in many instances is part of routine anaesthetic practice. It reduces the risk of hypoxia during apnoea after induction of anaesthesia by providing a reservoir of oxygen in the patient's functional residual capacity (FRC). Although there have been many studies on the period required for preoxygenation, none has measured alveolar gas concentration in the paediatric population. Recent work has established respiratory oxygraphy as a reliable and non-invasive measure of end-tidal oxygen fraction ($F\text{E}'_{O_2}$)[1 2]. The purpose of this study was to determine the duration of preoxygenation required in paediatric patients to achieve an $F\text{E}'_{O_2}$ of 0.9.

Patients and methods

After obtaining Ethics Committee approval, informed parental consent and patient assent, where appropriate, we studied 25 patients, aged 1–12 yr, ASA I–III, before induction of general anaesthesia. Premedication comprised midazolam 0.2 mg kg^{-1} intranasally at the discretion of the anaesthetist. Exclusion criteria included intracardiac shunting, active respiratory disease (including upper respiratory tract infection within 2 weeks), acute abdominal disease, known difficult airway or craniofacial abnormality such that an anaesthetic mask could not be applied to the face. Mean age was 4.1 (range 1–12) yr and mean weight was 20.9 (SD 14.2) kg.

A circle absorber system was flushed with 100% oxygen and a flow rate of 6 litre min^{-1} was used for the study. A clear anaesthetic face mask (Vital Signs, Totowa, USA) of appropriate size was used. Subjects were laid supine and the mask was applied to produce a gas tight seal. If old enough to understand, subjects were instructed to breathe normally. Inspired and expired gases were sampled from immediately adjacent to the mask by a Rascal II monitor (Ohmeda, Salt Lake City, USA) calibrated according to the manufacturer's instructions. This device uses the Raman light scattering principle to measure anaesthetic and respiratory gases with a response time of less than 350 ms (10–90% rise time). $F\text{E}'_{O_2}$ was recorded every 10 s and preoxygenation proceeded until $F\text{E}'_{O_2}$ reached 0.9.

Results

Mean (95% confidence limits) $F\text{E}'_{O_2}$ values were calculated for each 10-s period from the start of preoxygenation and used to construct a graph of oxygen wash-in against time (fig. 1). It was found that 22 (88%) of the subjects reached an $F\text{E}'_{O_2}$ of 0.9 within 60 s and all reached this end-point within 80 s.

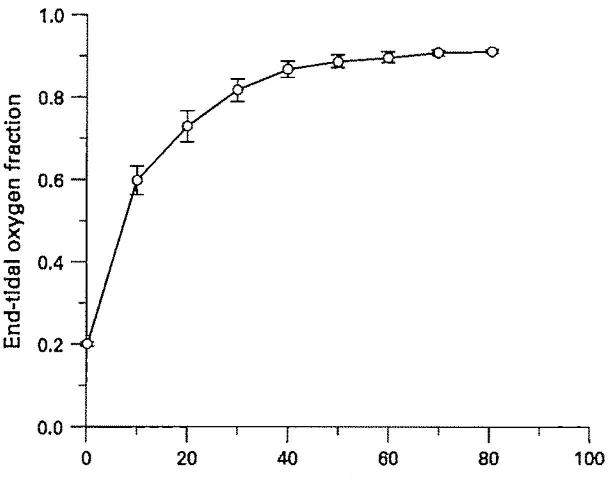

Figure 1 End-tidal oxygen fraction *vs* time for the 25 children during preoxygenation (mean, 95% confidence limits).

Discussion

There have been many studies of desaturation during induced apnoea after preoxygenation. Two studies of time for oxygen saturation to decrease to 90% in children showed that desaturation can occur rapidly, especially in small children, and that preoxygenation was useful in preventing this[3-4]. However, using time to desaturate is a poor method of defining the time required for adequate preoxygenation. Desaturation

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is affected not only by variations in oxygen wash-in to the lungs, but also by variables such as cardiac index and oxygen consumption[5]. It is also a delayed and retrospective measurement. Measurement of oxygen saturation during the preoxygenation process is of little value as saturation may be 99–100% while breathing room air.

End-tidal oxygraphy enables the anaesthetist to see on a breath-by-breath basis the success of the preoxygenation process. Studies in adults have shown that oxygen wash-in follows an exponential pattern and it has been proposed that the end-point for adequate preoxygenation should be an $F\mathrm{E}'_{\mathrm{O}_2}$ of 0.9[1 2]. The remaining 0.1 fraction consists mainly of carbon dioxide and nitrogen. Compared with pulse oximetry, an advantage of using respiratory oxygraphy lies in the fact that it is a real-time measurement and reveals variations in oxygen wash-in between patients. It is also a sensitive detector of poor mask fit in that air entrainment is recognized immediately and can be rectified[6].

We have shown that preoxygenation to an $F\mathrm{E}'_{\mathrm{O}_2}$ of 0.9 was possible within 80 s in all patients. This finding is in contrast with studies in 40 healthy adults[1] and 200 adult elective surgical patients[2] in whom 20% and 23%, respectively, of subjects had not reached an $F\mathrm{E}'_{\mathrm{O}_2}$ of 0.9 within 180 s. More rapid oxygen wash-in would be expected in children. Tidal volume, deadspace and FRC values in children are similar to those of adults when related to body size, but children have a higher ventilatory frequency[5]. Closing volumes are not reached during the course of normal expiration in children, unlike in the case of older adults.

Children may be less compliant than adults with a prolonged period of preoxygenation. Expired oxygraphy enables the anaesthetist to monitor alveolar gas concentrations precisely so that induction of anaesthesia can occur as soon as $F\mathrm{E}'_{\mathrm{O}_2}$ reaches the desired level. There is a theoretical benefit in continuing preoxygenation after an $F\mathrm{E}'_{\mathrm{O}_2}$ of 0.9 has been reached as poorly perfused organs may take longer to equilibrate with the alveolar oxygen fraction.

In summary, we have shown that all children attained an $F\mathrm{E}'_{\mathrm{O}_2}$ of 0.9 with 80 s of preoxygenation. We have also demonstrated the value of expired oxygraphy in the assessment of optimal preoxygenation on an individual patient basis. When suitable monitors are unavailable we suggest that a sensible duration of preoxygenation in healthy children should be not less than 60 s, paying attention to technique to produce a good mask seal and prevent air entrainment.

References

1. Berry CB, Myles PS. Preoxygenation in healthy volunteers: a graph of oxygen washin using end-tidal oxygraphy. *British Journal of Anaesthesia* 1994; 72: 116.
2. Machlin HA, Myles PS, Berry CB, Butler PJ, Story DA, Heath BJ. End-tidal oxygen measurement compared with patient factor assessment for determining preoxygenation time. *Anaesthesia and Intensive Care* 1993; 21: 409–413.
3. Videiera RLR, Neto PPR, Gomide do Amaral RV, Freeman JA. Preoxygenation in children: for how long? *Acta Anaesthesiologica Scandinavica* 1992; 36: 109–111.
4. Dupeyrat A, Dubreuil M, Ecoffey C. Preoxygenation in children. *Anesthesia and Analgesia* 1994; 79: 1027.
5. Fisher BJ, Carlo WA, Doershuk CF. Pulmonary function from infancy through adolescence. In: Scarpelli EM, ed. *Pulmonary Physiology: Fetus, Newborn, Child and Adolescent.* Philadelphia: Lea & Febiger, 1990; 421.
6. McGowan P, Skinner A. Preoxygenation—the importance of a good face mask seal. *British Journal of Anaesthesia* 1995; 75: 777–778.

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Intubating conditions and time course of rocuronium-induced neuromuscular block in children

T. FUCHS-BUDER AND E. TASSONYI

Summary

We have investigated the potential of rocuronium 0.6 mg kg^{-1} (2×ED$_{95}$) and 0.9 mg kg^{-1} (3×ED$_{95}$) for rapid sequence induction in 100 children, aged 3–7 yr. Intubating conditions with the two different doses of rocuronium were assessed in 70 children (n=35 in each group) undergoing elective surgery. Intubation was carried out by mimicking rapid sequence induction, and intubation conditions were evaluated according to a standard score. Intubating conditions were good to excellent in all 70 patients investigated (2×ED$_{95}$: excellent 29, good 6; 3×ED$_{95}$: excellent 33, good 2). In another 30 children (n=15 in each group), we examined the times of rocuronium-induced neuromuscular block using electromyography. Lag time and recovery index did not differ significantly between the two groups (lag time: 37 (SD 12) *vs* 33 (14) s; recovery index: 9 (3) *vs* 10 (4) min). Three times the ED$_{95}$ induced deeper neuromuscular block, 1 min after injection compared with 2×ED$_{95}$ (twitch height: 42 (24) *vs* 25 (19)%, respectively; P<0.05). The same was true for onset time (193 (47) *vs* 118 (23) s; P<0.01), clinical duration (21 (4) *vs* 34 (11) min; P<0.01) and duration to 75% recovery (30 (6) *vs* 44 (4) min; P<0.01). By mimicking rapid sequence induction, both doses of rocuronium offered clinically acceptable (good or excellent) intubating conditions. (*Br. J. Anaesth.* 1996;**77**:335–338)

Key words

Anaesthesia, paediatric. Children. Neuromuscular block, rocuronium. Anaesthetic techniques, induction. Measurement techniques, electromyography.

Rocuronium bromide is a new steroidal nondepolarizing neuromuscular blocking drug, related structurally to vecuronium. This compound is characterized by a rapid onset and intermediate duration of neuromuscular block[1,2]. The rapid onset of action of rocuronium was the subject of several investigations determining if this compound allows rapid sequence induction. In adult patients, good to excellent intubating conditions were reported[3-5]. Crul and colleagues found that increasing the dose of rocuronium from 0.6 to 0.9 mg kg^{-1} improved conditions for rapid sequence induction[6]. Unfortunately they did not provide any information on whether or not this increase changed the time course of neuromuscular block, a well known phenomenon with other neuromuscular blockers[7]. In four of 40 patients undergoing elective Caesarean section, Abouleish and colleagues found clinically unacceptable intubating conditions after administration of rocuronium 0.6 mg kg^{-1}[8]. Thus, this suggests that 2×ED$_{95}$ of rocuronium is not sufficient for rapid sequence induction. The only published study using rocuronium for intubation in children was reported by Woelfel and co-workers[9]. However, the use of rocuronium in children for rapid sequence induction has not been evaluated to date. This question is of clinical interest because of the recent controversy on the use of suxamethonium in children[10,11].

The aim of this study was to investigate intubating conditions with two different doses of rocuronium (0.6 and 0.9 mg kg^{-1}) in children. Intubating conditions were investigated by mimicking rapid sequence induction. In addition, we assessed the time course of rocuronium-induced neuromuscular block.

Patients and methods

The study was approved by the institutional Ethics Committee and informed consent was obtained from the children's parents. We studied 100 children, ASA I or II, aged 3–7 yr, undergoing elective surgery. Patients were excluded if they were known to have neuromuscular disease or were receiving medications known to influence neuromuscular function. All patients were premedicated with midazolam 0.2 mg kg^{-1} orally, 1 h before induction of anaesthesia.

We first assessed the quality of rocuronium neuromuscular block in the context of rapid sequence induction. Seventy patients were allocated randomly to one of two groups of 35, to receive either rocuronium 0.6 mg kg^{-1} (2×ED$_{95}$) or 0.9 mg kg^{-1} (3×ED$_{95}$). Anaesthesia was induced with alfentanil 10 μg kg^{-1} and thiopentone 5 mg kg^{-1} followed by the dose of rocuronium according to patient group. Rocuronium was injected over 5 s. Sixty seconds after the end of injection, the trachea was intubated in all patients by the same experienced anaesthetist blinded to the treatment. He assessed intubating conditions using the following criteria[3]: excellent=jaw relaxed, vocal cords abducted and

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immobile, and no diaphragmatic movement; good=jaw relaxed, vocal cords abducted and immobile, and some diaphragmatic movement; poor=jaw relaxed, vocal cords moving, and coughing; and inadequate=jaw not relaxed and vocal cords closed. Cricoid pressure was applied during insertion of the tube. In addition, intubation time (time from start of intubation until definitive placement of the oral tube) was determined in both groups.

In the second part of the study we investigated the time course of rocuronium-induced neuromuscular block, comparing doses of 2xED$_{95}$ with 3xED$_{95}$. Thirty children were allocated randomly to one of two groups of 15. In both groups anaesthesia was induced with alfentanil 10 μg kg^{-1} and thiopentone 5 mg kg^{-1}, and maintained with isoflurane (1% end-tidal concentration) and 60% nitrous oxide in oxygen via a face mask. End-tidal carbon dioxide concentration was maintained at 4.5–5 vol% (Normocap, Datex Instrumentarium Corporation, Finland). Neuromuscular transmission was assessed by electromyography (Relaxograph, Datex Instrumentarium Corporation, Finland) at the right ulnar nerve–hypothenar muscle using transcutaneous electrodes. Measurements started when anaesthesia had been induced. The Relaxograph was set to deliver supramaximal stimuli (0.1 ms duration) of train-of-four (TOF) at 2 Hz every 20 s. The first of the four evoked responses was considered the twitch height. To minimize movement-induced changes in twitch response during electromyography, the patient's hand was fixed carefully. When the end-tidal isoflurane concentration had stabilized, the Relaxograph was re-calibrated and control twitch height measured. Patients then received either rocuronium 0.6 or 0.9 mg kg^{-1}. Administration of rocuronium was synchronized with the Relaxograph, with completion of injection concomitantly at the end of control TOF stimulation. The following times of neuromuscular block were measured: lag time=time between administration of rocuronium and the first measurable neuromuscular effect (twitch depression ≥5% of control value); twitch height at 1 min = twitch height 1 min after administration of rocuronium; onset time=time between administration of rocuronium and maximum twitch depression; clinical duration (CD)=time between administration of rocuronium and recovery to 25% twitch height; recovery index (RI)=time from 25% to 75% twitch height recovery; and duration 75 (D75)=time between administration of rocuronium and recovery to 75% twitch height.

End-tidal carbon dioxide concentration, temperature over the adductor pollicis muscle and isoflurane concentration were maintained stable during the whole study (4.5–5 vol%, ≥35 °C and 0.8–1%, respectively). Patients did not receive additional neuromuscular blockers until recovery to 95±5% twitch height. Patients in whom twitch height did not recover to control levels were excluded.

The Mann–Whitney *U* test was used for statistical comparison of the times of neuromuscular block induced by the two different doses of rocuronium. Intubating conditions were analysed using the chi-square test. All values, except intubation scores, are expressed as mean (SD). For statistical comparisons, differences were considered significant when $P<0.05$.

Table 1 Patient data (mean (SD or range))

	Intubating conditions		Time course	
Rocuronium	0.6 mg kg^{-1}	0.9 mg kg^{-1}	0.6 mg kg^{-1}	0.9 mg kg^{-1}
n	35	35	15	15
Age (yr)	5 (3–7)	5 (3–7)	5 (3–7)	5 (3–7)
Weight (kg)	20.7 (4.8)	20.9 (4.5)	20.7 (3.3)	19.7 (3.4)

Table 2 Rapid sequence induction: intubating conditions. Intubation score: Excellent=jaw relaxed, vocal cords abducted and immobile, and no diaphragmatic movement; Good=jaw relaxed, vocal cords abducted and immobile, and some diaphragmatic movement; Poor=jaw relaxed, vocal cords moving, and coughing; Inadequate=jaw not relaxed and vocal cords closed; Intubating time=time from beginning of intubation until placement of the oral tube

	Rocuronium	
	0.6 mg kg^{-1} (n=35)	0.9 mg kg^{-1} (n=35)
Intubation score		
Excellent	29	33
Good	6	2
Poor	0	0
Inadequate	0	0
Intubating time (s) (mean (SD))	12.5 (3.4)	11.6 (2.7)

Table 3 Rapid sequence induction: effective dose of drugs used (mean (SD))

	Rocuronium	
	0.6 mg kg^{-1}	0.9 mg kg^{-1}
Thiopentone (mg kg^{-1})	5.0 (0.18)	4.99 (0.17)
Alfentanil (μg kg^{-1})	9.78 (0.75)	9.94 (0.63)
Rocuronium (mg kg^{-1})	0.60 (0.02)	0.90 (0.02)

Results

The study groups did not differ in age or weight (table 1).

Intubating conditions obtained with both rocuronium 2xED$_{95}$ and 3xED$_{95}$ were clinically acceptable (e.g. excellent or good) (table 2). There were no differences in the frequency distribution of excellent or good intubation conditions between the two groups: after 2xED$_{95}$, intubating conditions were excellent in 29 patients and good in six; after 3xED$_{95}$, intubating conditions were excellent in 33 patients and good in two. Intubation was performed within 12.5 (3.4) s after 2xED$_{95}$ and within 11.6 (2.7) s after 3xED$_{95}$. The doses of drugs used for rapid sequence induction were comparable in both groups (table 3): thiopentone (5.0 (0.18) *vs* 4.99 (0.17) mg kg^{-1}) and alfentanil (9.78 (0.75) *vs* 9.94 (0.63) μg kg^{-1}; respectively).

After rocuronium, twitch height recovered to control levels in all 30 patients included in this part of the study. Lag time did not differ between the two doses (37 (12) *vs* 33 (14) s; respectively) but after 3 × ED$_{95}$ onset time was found to be faster (193 (47) *vs* 118 (23) s; $P<0.01$), clinical duration longer (21 (4) *vs* 34 (11) min; $P<0.01$), duration until 75% recovery of twitch height longer (30 (6) *vs* 44 (4) min; $P<0.01$) and neuromuscular block at 1 min greater (42 (24) *vs* 25 (19)% twitch height, $P<0.05$).

Table 4 Time course of neuromuscular block (mean(SD)). Lag time = Time between injection of the neuromuscular blocker and first measurable neuromuscular effect; Onset time = Time between injection of the neuromuscular blockers and maximal block; Twitch height at 1 min = Twitch height 1 min after the end of injection of the neuromuscular blocker; CD = Clinical duration; RI = Recovery index; D75 = Duration until 75% recovery of twitch height; $^{*}P < 0.05$; $^{**}P < 0.01$

	Rocuronium	
	0.6 mg kg^{-1} (n=35)	0.9 mg kg^{-1} (n=35)
Lag time (s)	37 (12)	33 (14)
Onset time (s)	193 (47)	118 (23)**
Twitch height at 1 min (%)	42 (24)	25 (19)*
CD (min)	21 (4)	34 (11)**
RI (min)	9 (3)	10 (4)
D75 (min)	30 (6)	44 (4)**

Recovery index was similar in both groups: 9 (3) min after 2xED_{95} and 10 (4) min after 3xED_{95} (table 4).

Discussion

We have investigated for the first time the potential of rocuronium for rapid sequence induction in children. The doses of rocuronium represented 2xED_{95} and 3xED_{95} for this age group[9]. The most important finding was that after both rocuronium 2xED_{95} (0.6 mg kg^{-1}) and 3xED_{95} (0.9 mg kg^{-1}), intubating conditions evaluated at 60 s after administration of the neuromuscular blocking agent were good to excellent (table 2).

There is some controversy on whether or not measurement of end-points such as onset time is meaningful in the context of defining optimal intubating conditions. Agoston stated that "onset time has become overestimated as a predictive parameter for the rate of development of adequate intubating conditions", and "is not a meaningful, quantifiable end-point defining optimal intubating conditions"[12]. Conversely, Magorian, Flannery and Miller "have chosen to monitor twitch tension as an end-point defining optimal intubating conditions, because this technique is quantifiable and reliable"[5]. Intubation score is the principal measure in the context of rapid sequence induction, as it indicates whether or not the patient's airway can be adequately secured reliably. Measurement of the time course of neuromuscular block is also important because information on onset characteristics (e.g. lag time, twitch height at 1 min and onset time) are complementary to information provided by the intubation score. However, both intubating conditions and time course of neuromuscular block are influenced by the depth of anaesthesia[8 13]. To overcome this problem in the context of measurement of the time course of neuromuscular block, re-calibration of the Relaxograph is needed when steady state concentration of the volatile anaesthetic is achieved. Any additional change in inspired concentration may directly influence the results[14] thus compromising the relevance of the data. With regard to intubating conditions, only those drugs needed for rapid sequence induction should be given, with no drug supplement before the tracheal tube is inserted and intubating conditions scored[15]. We evaluated both intubation score and times of rocuronium-induced neuromuscular block. In order to overcome the methodological problem described, we evaluated intubating conditions and neuromuscular pharmacodynamics in separate groups of patients.

Thus in the first part of the study we investigated the potential of rocuronium for rapid sequence induction, using it strictly according to the scenario for rapid sequence induction but in elective cases. Factors affecting intubation conditions, such as the dose of hypnotic[16] or opioid[17], were controlled in a very narrow range (table 3), and were comparable between both groups. No volatile anaesthetic or other drug supplement was given until after intubation. In all 70 patients, the trachea was intubated rapidly and without difficulty, and intubating conditions were clinically acceptable (table 2). In the group receiving 3xED_{95}, a trend towards a higher frequency of excellent intubating conditions was found. However, this difference was not statistically significant.

It would be of interest to compare intubating conditions after rocuronium with those after suxamethonium, the gold standard for rapid sequence induction. However, in view of the controversy on the use of this compound in elective paediatric anaesthesia[10 11], and clinical practice in our institution which limits suxamethonium to paediatric emergencies, we dismissed this possibility. In our opinion, these two drugs should be compared in children undergoing emergency intubation, where the use of suxamethonium is generally accepted.

To date, there are few data available on intubating conditions with rocuronium in paediatric patients. In a study of 12 children, intubating conditions 60 s after rocuronium were found to be excellent in nine and good in three patients[9]. Unfortunately the authors did not provide information on the potential of rocuronium for rapid sequence intubation, as intubating conditions were evaluated under steady state halothane anaesthesia. In adults, there is one published investigation on the potential of rocuronium for emergency intubation, using it strictly according to the scenario for rapid sequence induction but still in elective cases[6]. These authors found a higher frequency of excellent intubating conditions when the dose of rocuronium was increased from 0.6 to 0.9 mg kg^{-1}. They concluded that the higher dose of rocuronium should be used for "real" rapid sequence induction. This conclusion was supported indirectly by the results of Abouleish and colleagues who found in four of 40 patients undergoing Caesarean section poor or inadequate intubation conditions 60 s after rocuronium 0.6 mg kg^{-1}[8].

In the second part of this study, we measured the time course of neuromuscular block after rocuronium 0.6 and 0.9 mg kg^{-1} in children. Particular attention was given to assessing the onset characteristics of rocuronium. These were assessed measuring lag time, twitch height at 1 min and onset time. In a study in adult patients, Wierda and colleagues[18] found that the lag time of rocuronium was less than that of vecuronium; neuromuscular block was initiated in less than 40 s, which is important in situations where rapid control of the airway is required. However, in this study, an increase in the dose of rocuronium from 0.6 to 0.9 mg kg^{-1} did not lead to further acceleration of lag time. In addition, the initial progression of rocuronium-induced neuromuscular block was fast, leading to advanced motor block 1 min after injection of rocuronium, at the moment when rapid sequence intubation takes place. This phenomenon was more pronounced after the higher dose. In contrast with these findings, the onset time of rocuronium was not particularly fast in our patients. This confirms the findings of Wierda and colleagues who reported that rocuronium has an onset time comparable with that of vecuronium[18]. It is the rapid initial development of neuromuscular block which distinguishes rocuronium from other non-depolarizing neuromuscular blocking agents, and this may explain the favourable intubating conditions observed.

The duration of action of rocuronium was found to be intermediate after both 0.6 and 0.9 mg kg^{-1} (table 4). Increasing the dose of rocuronium also increased its duration of action. This increase was statistically significant, but should not be clinically relevant as the profile of the drug did not change. Moreover, the recovery index was not affected by the increase in dose. These results are in accordance with those reported in the same age group by Woelfel and colleagues[9].

We conclude that in children, rocuronium at both doses investigated offered good to excellent intubating conditions for rapid sequence induction in elective patients. Whether or not the intubating conditions of either rocuronium 0.6 or 0.9 mg kg^{-1} are comparable with those of suxamethonium should be investigated in real emergency situations.

References

1. Mayer M, Doenicke A, Hofmann A, Peter K. Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 511–512.
2. Bartowski RR, Witkowski TA, Azad S, Lessin J, Marr A. Rocuronium onset of action: a comparison with atracurium and vecuronium. *Anesthesia and Analgesia* 1993; **77**: 574–578.
3. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adults. *Anesthesiology* 1993; **79**: 913–918.
4. Pühringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1992; **75**: 37–40.
5. Cooper R, Mirakhur RK, Clake RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–273.
6. Crul JF, Vanbelleghem V, Buyse L, Heylen R, van Egmond J. Rocuronium with alfentanil and propofol allows intubation within 45 seconds. *European Journal of Anaesthesiology* 1995; 12 (Suppl.11): 111–112.
7. Ginsberg B, Glass PS, Quill T, Shafron D, Ossey KD. Onset and duration of neuromuscular blockade after high-dose vecuronium administration. *Anesthesiology* 1989; **71**: 201–205.
8. Abouleish E, Abboud T, Lechevalier T, Zhu J, Challian A, Alford K. Rocuronium (Org 9426) for Caesarean section. *British Journal of Anaesthesia* 1994; **73**: 336–341.
9. Woelfel SK, Brandom BW, Cook R, Sarner J B. Effects of bolus administration of Org-9426 in children during nitrous oxide–halothane anesthesia. *Anesthesiology* 1992; **76**: 939–942.
10. Belmont MR. Succinylcholine/suxamethonium. *Current Opinion in Anesthesiology* 1995; **8**: 362–366.
11. Hopkins PM. Use of suxamethonium in children. *British Journal of Anaesthesia* 1995; **75**: 675–677.
12. Agoston S. Onset time and evaluation of intubating conditions: rocuronium in perspective. *European Journal of Anaesthesiology* 1995; **12** (Suppl.11): 31–37.
13. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. *Anesthesiology* 1984; **60**: 102–105.
14. Wright PMC, Hart P, Lau M, Brown R, Sharma ML, Gruenke L, Fisher DM. The magnitude and time course of vecuronium potentiation by desflurane versus isoflurane. *Anesthesiology* 1995; **82**: 404–411.
15. Fuchs-Buder T, Wilder-Smith OHG, Borgeat A, Tassonyi E. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. *British Journal of Anaesthesia* 1995; **74**: 405–409.
16. Hovorka J, Honkavaara P, Korttila K. Tracheal intubation after induction of anaesthesia with thiopentone or propofol without muscle relaxants. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 326–328.
17. Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. *Anesthesia and Analgesia* 1992; **75**: 788–793.
18. Wierda JMKH, De Wit APM, Kuizenga K, Agoston S. Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent. *British Journal of Anaesthesia* 1990; **64**: 521–523.

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Influence of induction technique on intubating conditions after rocuronium in adults: comparison with rapid-sequence induction using thiopentone and suxamethonium

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Summary

We have assessed the effect of anaesthetic technique on intubating conditions after rocuronium 0.6 mg kg^{-1} in four groups (n=25 each) of unpremedicated patients in whom anaesthesia was induced with either thiopentone 5 mg kg^{-1} or propofol 2.5 mg kg^{-1} alone, or supplemented with alfentanil 20 μg kg^{-1}. Fifty control patients were anaesthetized with thiopentone followed by suxamethonium. Laryngoscopy was commenced at 45 s. Overall intubating conditions after rocuronium were similar to those after suxamethonium (good and excellent ≥96%) only when alfentanil was part of the induction regimen. However, intubation time was similar in all five groups and averaged 55 (SD 3.2) s, and the tube could be passed through open vocal cords within 70 s. After rocuronium the response of the diaphragm to intubation was more pronounced in the two groups of patients not receiving alfentanil (P<0.0001) and in patients anaesthetized using propofol with alfentanil (P<0.01) than in the control group. Opioids (in doses equivalent to alfentanil 20 μg kg^{-1}) constitute an integral part of an induction regimen containing rocuronium 0.6 mg kg^{-1}, regardless of whether or not thiopentone or propofol is used, in order to achieve overall intubating conditions similar to those after suxamethonium. (*Br. J. Anaesth.* 1996;**77**:339–342)

Key words

Anaesthetic techniques, induction. Intubation, tracheal. Neuromuscular block, rocuronium. Neuromuscular block, suxamethonium. Anaesthetics i.v., thiopentone. Analgesics opioid, alfentanil.

Rocuronium offers the fastest onset of action of all clinically available non-depolarizing neuromuscular blocking agents. Intubating conditions at 60 s after administration of rocuronium 0.6 mg kg^{-1} have been reported to be similar to those after suxamethonium[1–3]. This similarity in intubating conditions is surprising, because the onset of action of rocuronium at the laryngeal adductor muscles is slower than that after suxamethonium, and the degree of block at these muscles is less intense[4].

Anaesthetic techniques used in previous studies[1–3], in particular the use of opioids, may have improved intubating conditions after rocuronium. When increasing doses of opioids were added to propofol, intubating conditions were similar to those after suxamethonium, even in the absence of a neuromuscular blocking agent[5 6]. Propofol rather than thiopentone may further facilitate intubation, as propofol was shown to depress laryngeal reflexes to a greater extent than thiopentone in comparable doses[7]. When anaesthesia was induced with thiopentone alone in unpremedicated adult patients, intubating conditions produced by rocuronium were less favourable than those produced by suxamethonium[8].

Consequently, we hypothesized that opioids should be used with an induction regimen containing rocuronium in order to achieve tracheal intubation within 60 s. In addition, we were interested in whether or not intubating conditions after rocuronium are more favourable if anaesthesia is induced with thiopentone rather than with propofol. Therefore, in this study we administered rocuronium to four groups of unpremedicated patients in whom anaesthesia was induced in a rapid-sequence manner, either with thiopentone or propofol alone, or supplemented with the opioid alfentanil. Rapid-sequence induction with thiopentone and suxamethonium was used in a control group.

Patients and methods

The study was approved by the Ethics Committee of the Medical Faculty of the University of Innsbruck. After obtaining written, informed patient consent, we studied 150 subjects, ASA I–II, aged 18–65 yr, undergoing minor elective surgery (orthopaedic or gynaecological) under general anaesthesia. None of the patients had a history of malignant hyperthermia or were receiving any medications known to interact with neuromuscular blocking agents. Pregnant patients were excluded. A careful physical examination was performed to exclude patients with potential airway problems.

STUDY DESIGN

Patients were allocated randomly to one of five study groups. In the control group, 50 patients received

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thiopentone 5 mg kg^{-1} and suxamethonium 1 mg kg^{-1} in a rapid-sequence manner. Rocuronium 0.6 mg kg^{-1}, twice its ED95, was administered to four other groups of patients (25 patients in each group) in whom anaesthesia was induced with either thiopentone 5 mg kg^{-1} (group T-R) or propofol 2.5 mg kg^{-1} (group P-R) alone, or supplemented with alfentanil 20 μg kg^{-1} (groups AT-R and AP-R). The main variables assessed in these patients were intubation time and intubating conditions.

ANAESTHETIC TECHNIQUE

Patients did not receive premedication. After 3 min of preoxygenation, anaesthesia was induced in a rapid-sequence manner (not applying cricoid pressure) with thiopentone or propofol followed by suxamethonium or rocuronium. When alfentanil was part of the induction technique, it was administered immediately before the i.v. anaesthetic. All drugs were given into a rapidly running infusion of lactated Ringer's solution. Injection times were 10 s for alfentanil and thiopentone, 15 s for propofol, and less than 5 s for rocuronium and suxamethonium. Heart rate (determined by ECG), non-invasive arterial pressure, arterial oxygen saturation (Sp_{O_2}) and endtidal carbon dioxide concentration were monitored in all patients (Cardiocap, Datex, Finland).

TRACHEAL INTUBATION

A tracheal tube (Mallinckrodt Lo-Pro, Mallinckrodt Laboratories, UK) with an internal diameter of 8.5 cm in males and 7.5 cm in females was used. A flexible plastic mounted stylet was inserted into the tube. The same fully trained anaesthetist ("intubator"), who was blinded to the treatment each patient received, performed all intubations using a Macintosh size 4 blade. In order to prevent the intubator from noting suxamethonium-related muscle fasciculations, the intubator was called to enter the study room 40 s after administration of the blocker, and another 5 s later he was instructed to start intubation. The tube was intended to be placed in the trachea as soon as possible, but only when the vocal cords were open and immobile. Otherwise insertion of the tube was delayed until the vocal cords were open and immobile.

ASSESSMENT OF INTUBATION TIME AND INTUBATING CONDITIONS

Intubation time was recorded as the number of seconds from the end of administration of blocker to insertion of the tube in the trachea, as measured by a stop-watch. Intubating conditions were assessed using the criteria of Cooper and colleagues[9] (table 1). In addition, the occurrence of suxamethonium-related muscle fasciculations and movement of the limbs during and immediately after intubation were noted by both the attending anaesthetist and the intubator.

STATISTICAL ANALYSIS

Summary statistics (sample size, mean (SD)) were calculated for all quantitative variables of each group. We used one-way analysis of variance to compare age, weight and height between the five groups, and the chi-square test to compare distribution by sex. In order to evaluate differences between the control and each of the other groups, intubation time was analysed using the Mann–Whitney *U* test, and intubating conditions assessed using the chi-square or Fisher's exact test. Estimation of sample size was based on the results of a previous study[8] in which 60% of patients receiving rocuronium and 92% of patients receiving suxamethonium showed excellent intubating conditions after rapid-sequence induction with thiopentone. Using a two-group chi-square test (0.05 two-sided significance level with a correction factor for the four comparisons, 80% power) the minimum sample size thus determined was 45 patients for the control and 23 patients for each of the groups given rocuronium. Calculations were carried out using the software package SPSS (version 6.0 for Windows, SPSS Inc., Chicago, IL, USA).

Table 1 Scoring of intubating conditions[9]. A total score of 8–9 = excellent; 6–7 = good; 3–5 = fair; 0–2 = poor

Score	Jaw relaxation (ease of laryngoscopy)	Vocal cords	Response to intubation
0	Poor (impossible)	Closed	Severe coughing or bucking
1	Minimal (difficult)	Closing	Mild coughing
2	Moderate (fair)	Moving	Slight diaphragmatic movement
3	Good (easy)	Open	None

Results

Mean age, weight and height of the 150 patients were 34 (range 18–55) yr, 69 (SD 12.0) kg and 172 (8.7) cm.

Intubation time was similar in all groups with a mean value of 55.0 (3.4) s. In seven patients (two patients in the control group, three in group T-R, and one each in groups P-R and AT-R) the tube was positioned after 60 s because of problems with laryngoscopy or closed and mobile vocal cords. However, in all patients the tracheal tube was passed easily through open vocal cords within 70 s. Intubating conditions approximately 60 s after suxamethonium (control group) were rated as excellent in 88% and good in 12% of patients. Intubating conditions 60 s after rocuronium differed between the control and groups T-R and P-R, but were similar between the control and groups AT-R and AP-R, in which alfentanil was given during induction of anaesthesia. In groups T-R and P-R, intubating conditions were rated as excellent in only 40% and 32%, good in 40% and 60%, and fair in 20% and 8% of patients, respectively ($P<0.0001$ *vs* control) (fig. 1).

Among the three variables contributing to assessment of intubating conditions, ease of laryngoscopy was similar in all patients. On average, laryngoscopy was judged to be easy in 80% and fair in 20% of patients. However, the condition of the vocal cords differed between the control group and rocuronium-treated patients who did not receive alfentanil (fig. 2). In addition, in groups T-R and P-R and also in

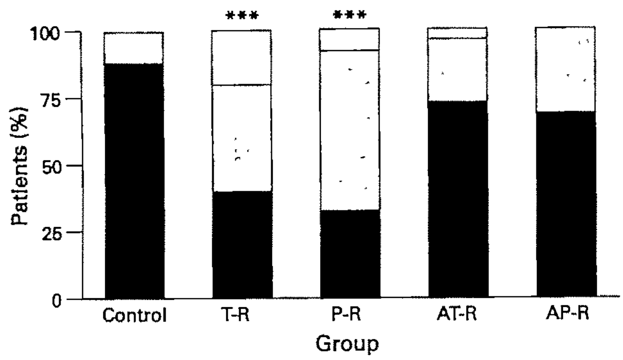

Figure 1 Intubating conditions after suxamethonium (control group; n=50) or rocuronium (groups T-R, P-R, AT-R and AP-R; n=25 each) after rapid-sequence induction using different anaesthetic techniques. (Solid bars=excellent, shaded bars=good, open bars=fair.) ***P<0.0001 compared with control value.

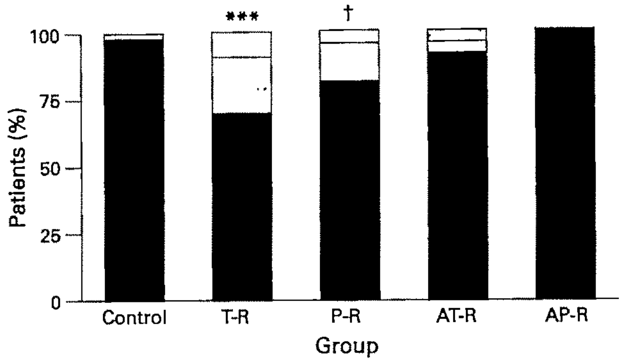

Figure 2 Initial aspect of the vocal cords on laryngoscopy, ≥45 s after suxamethonium (control group; n=50) or rocuronium (groups T-R, P-R, AT-R and AP-R; n=25 each) after rapid sequence induction using different anaesthetic techniques. (Solid bars=open, lightly shaded bars=moving, open bars=closing, darkly shaded bars=closed.) ***P<0.001, group T-R compared with control; †P < 0.05, group P-R compared with control.

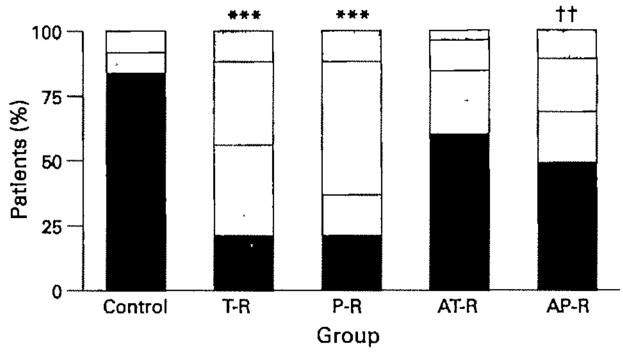

Figure 3 Response of the diaphragm to intubation after suxamethonium (control group; n=50) or rocuronium (groups T-R, P-R, AT-R and AP-R; n=25 each) after rapid-sequence induction with different anaesthetic techniques. (Solid bars=none, lightly shaded bars=diaphragmatic movement, open bars=mild coughing, darkly shaded bars=severe coughing.) ***P<0.0001, groups T-R and P-R compared with control; ††P<0.01, group AP-R compared with control.

group AP-R, the response of the diaphragm to intubation was more pronounced than in the control group (fig. 3).

Suxamethonium-related muscle fasciculations were not seen by the intubator, whereas the attending anaesthetist observed muscle fasciculations in 85% of patients given suxamethonium. During or immediately after intubation, or both, movement of the limbs (most frequently the hand, lower arm and foot) were observed in 8% of patients after suxamethonium, but in 40% of patients in group T-R (P<0.002 *vs* control), and 56% of patients in group P-R (P<0.001 *vs* control). In contrast, there was no difference in the incidence of movement of the limbs between the control and groups AT-R and AP-R, who were given alfentanil during induction.

Discussion

The results of this study indicated that in unpremedicated adult patients, intubating conditions after rocuronium were influenced by the induction technique. However, the anaesthetic technique used for induction of anaesthesia had no significant influence on intubation time after rocuronium 0.6 mg kg^{-1} compared with suxamethonium. Overall intubating conditions after rocuronium were similar to those after suxamethonium when alfentanil 20 μg kg^{-1} was part of the induction regimen. However, they differed from those after suxamethonium when anaesthesia was induced with either thiopentone or propofol alone in equipotent doses[10].

The findings of this study are supported by the results of previous studies in which intubating conditions after rocuronium were assessed. In one group of studies, where opioids were part of the induction regimen or used for premedication, intubating conditions at 60 s after rocuronium 0.6 mg kg^{-1} were similar to those after suxamethonium[1-3]. Although opioids and i.v. anaesthetics had no influence on the neuromuscular blocking effects of rocuronium[11], the use of opioids in these studies might have contributed to the favourable intubating conditions 60 s after rocuronium. After addition of increasing doses of alfentanil to propofol or thiopentone, both used as induction agents, intubating conditions became more favourable[6 12] and were even similar to those after suxamethonium[5 6]. However, when no neuromuscular blocking agent was administered, intubation failed in 50% of patients anaesthetized with propofol 1.5–2 mg kg^{-1} and alfentanil 1 mg^{1}.

In another set of two studies, intubating conditions were found to be less favourable after rocuronium than after suxamethonium[8 9]. In one of these studies, in unpremedicated adult patients, anaesthesia was induced in a rapid-sequence manner with thiopentone alone (6 mg kg^{1})[8]. In the other, patients were premedicated orally, and anaesthesia was induced with small doses of thiopentone and fentanyl and maintained with increments of these agents for approximately 10 min before rocuronium was administered[9].

Evidence suggesting that anaesthesia does have an impact on intubating conditions after rocuronium is supported by the findings of another study on rocuronium, in patients undergoing Caesarean section. The dose of thiopentone was increased from 4 to 6 mg kg^{-1}, and intubation was commenced at 80 s instead of 60 s in order to achieve good or excellent intubating conditions in 90% of patients[13].

In contrast with other investigators[1-3 9], we did not measure the time course of action of rocuronium, as the main purpose of this study was to challenge the efficacy of rocuronium in providing smooth intubating conditions within 60 s by using different techniques of induction of anaesthesia. In addition, until now no conclusive correlation between onset time at the adductor pollicis muscle and intubating conditions has been shown[14]. In our study, laryngoscopy revealed that the vocal cords were moving or closing in about 25% of rocuronium-treated patients who did not receive alfentanil during induction. The response of the diaphragm to intubation was more pronounced after rocuronium than after suxamethonium, but was attenuated by alfentanil (fig. 3).

These findings are supported by recent investigations[4 15 16]. The laryngeal adductor muscles and the diaphragm are more resistant to the effects of rocuronium than the adductor pollicis muscle[15 16]. However, the onset of action of small doses of rocuronium (0.4 and 0.5 mg kg^{-1}) at the laryngeal adductor muscles was shown to be faster than at the adductor pollicis muscle[4 16]. In contrast, the onset of rocuronium at the diaphragm was found to be slower than at the adductor pollicis muscle[15]. In addition, even after administration of higher doses of rocuronium (0.8 and 1.2 mg kg^{-1}), the onset of action at the laryngeal adductor muscles was slower than that after suxamethonium 1 mg kg^{-1} [4].

Hence, signs of incomplete neuromuscular block at the vocal cords, the diaphragm and other muscles may be observed more frequently after administration of rocuronium 0.6 mg kg^{-1} than after suxamethonium, if laryngoscopy with subsequent tracheal intubation is commenced at 45 s, in particular with a light plane of anaesthesia. In this study, movement of the limbs was noted only in exceptional cases after suxamethonium, and after rocuronium with alfentanil, but were observed frequently (≥40%) after rocuronium without alfentanil.

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References

1. Huizinga ACT, Vandenbrom RHG, Wierda JMKH, Hommes FDM, Hennis PJ. Intubating conditions and onset of neuromuscular block of rocuronium (Org 9426); a comparison with suxamethonium. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 463–468.
2. Pühringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1992; **75**: 37–40.
3. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology* 1993; **79**: 913–918.
4. Wright PM, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. *Anesthesiology* 1994; **81**: 1110–1115.
5. Beck BN, Masterson GR, Richards J, Bunting P. Comparison of intubation after propofol and alfentanil with intubation after thiopentone and suxamethonium. *Anaesthesia* 1993; **48**: 876–880.
6. Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: A technique using propofol and varying doses of alfentanil. *Anesthesia and Analgesia* 1992; **75**: 788–793.
7. McKeating K, Bali IM, Dundee JW. The effects of thiopentone and propofol on upper airway integrity. *Anaesthesia* 1988; **43**: 638–640.
8. Sparr HJ, Luger TJ, Heidegger T, Putensen-Himmer G. Comparison of intubating conditions after rocuronium and suxamethonium after 'rapid-sequence induction' with thiopentone in elective cases. *Acta Anaesthesiologica Scandinavica* 1996; **40**: 425–430.
9. Cooper R, Mirakhur RK, Clarke RS, Boules Z, Clarke RSJ. Comparison of intubating conditions after administration of Org 9246 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–273.
10. Van Hemelrijck J, Muller P, Van Aken H, White PF. Relative potency of eltanolone, propofol, and thiopental for induction of anesthesia. *Anesthesiology* 1994; **80**: 36–41.
11. Olkkola KT, Tammisto T. Quantifying the interaction of rocuronium (Org 9426) with etomidate, fentanyl, midazolam, propofol, thiopental, and isoflurane using closed-loop feedback control of rocuronium infusion. *Anesthesia and Analgesia* 1994; **78**: 691–696.
12. Helbo-Hansen S, Ravlo O, Trap-Andersen S. The influence of alfentanil on the intubating conditions after priming with vecuronium. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 41–44.
13. Abouleish E, Abboud T, Lechevalier T, Zhu J, Chalian A, Alford K. Rocuronium (Org 9426) for Caesarean section. *British Journal of Anaesthesia* 1994; **73**: 336–341.
14. Agoston S. Onset time and evaluation of intubating conditions: rocuronium in perspective. *European Journal of Anaesthesiology* 1995; **12** (Suppl. 11): 31–37.
15. Cantineau JP, Porte F, D'Honneur G, Duvaldestin P. Neuromuscular effects of rocuronium on the diaphragm and adductor pollicis muscles in anesthetized patients. *Anesthesiology* 1994; **81**: 585–590.
16. Plaud B, Proost JH, Wierda JM, Barre J, Debaene B, Meistelman C. Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans. *Clinical Pharmacology and Therapeutics* 1995; **58**: 185–191.

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Spinal anaesthesia with 0.5% hyperbaric bupivacaine in elderly patients: effect of site of injection on spread of analgesia

B. Th. Veering, P. M. Ter Riet, A. G. L. Burm, R. Stienstra and J. W. van Kleef

Summary

In this randomized, observer-blind study, we have examined, in elderly patients, the effect of site of injection on analgesia levels after spinal injection of 0.5% hyperbaric bupivacaine solution. Thirty male patients, aged 68–87 yr, undergoing minor urological surgery during spinal anaesthesia received 3 ml of a 0.5% hyperbaric bupivacaine solution at either the L3–4 (n=15) or L4–5 (n=15) interspace. The solution was injected with the patient in the sitting position. The patient remained sitting for 2 min and was then placed in the supine horizontal position. Analgesia levels were assessed bilaterally using pinprick. The highest analgesia levels did not differ between groups (medians were approximately T7). There were no significant differences in the time to maximum cephalad spread of analgesia, maximum degree of motor block or haemodynamic changes. We conclude that injection at the L4–5 interspace has no advantage compared with injection at the L3–4 interspace. (*Br. J. Anaesth.* 1996;**77**:343–346)

Key words

Anaesthetic techniques, subarachnoid. Anaesthetics local, bupivacaine. Age factors.

Clinical studies have shown that the profile of spinal anaesthesia after subarachnoid administration of hyperbaric bupivacaine solutions changes with increasing age[1–3]. The highest level of analgesia extends approximately 3–4 segments higher in elderly compared with young adult patients. Age and higher levels of analgesia appear to be the main factors associated with the development of hypotension during spinal anaesthesia[4]. The degree of arterial hypotension after subarachnoid administration of local anaesthetics correlates with the level of sympathetic block, which is generally 2–4 spinal segments higher than the level of analgesia[5]. Therefore, it is important to limit the levels of analgesia and the associated levels of sympathetic block. This study was designed to determine and compare the levels of analgesia after injection of a hyperbaric bupivacaine solution at the L3–4 or L4–5 interspaces.

Patients and methods

We studied 30 male patients, ASA I–III, aged 68–87 yr, undergoing minor urological surgery under spinal anaesthesia. The study was approved by the Medical Ethics Committee of the University Hospital Leiden and verbal consent was obtained from all patients. Patients with diabetes, a history of neurological disease or coagulopathy were excluded. Patients were allocated randomly to receive 0.5% hyperbaric bupivacaine solution at either the L3–4 (group 1, n=15) or L4–5 (group 2, n=15) lumbar interspace. A randomization table was made before the start of the study and codes were stored in sealed envelopes, which were opened shortly before the extradural procedure.

Patients were premedicated with temazepam 10 mg orally and atropine 0.25 mg i.m., 45 min before induction of spinal anaesthesia. Before spinal injection, 500 ml of glucose in saline were administered by rapid i.v. infusion. The appropriate lumbar interspace was determined independently by two anaesthetists. The spines of the vertebrae were counted from both the cranial and caudal directions and the iliac crest was palpated to confirm the position of the fourth lumbar vertebra. Dural puncture was performed with the patient in the sitting position by a standard midline approach using a 25-gauge Quincke spinal needle via an 18-gauge introducer. When a free flow of clear cerebrospinal fluid was obtained and after aspiration of 0.2 ml of spinal fluid, 0.5% bupivacaine HCl 3 ml in 8% glucose (Marcaine heavy, Astra, Södertälje, specific gravity 1.026 at 20 °C) was injected at room temperature at a rate of 0.2 ml s^{-1}. Patients were kept sitting for 2 min after completion of the subarachnoid injection and were then placed in the supine horizontal position.

Analgesia was assessed bilaterally in the anterior axillary line by pinprick using a short bevelled 25-gauge needle. Assessments were made every 5 min during the first 30 min after injection and at 45 and 60 min thereafter. Analgesia was defined as inability to detect a sharp pinprick. When maximum cephalad spread of analgesia was produced, motor block of the lower limbs was assessed bilaterally using a modified Bromage classification by asking the patient to raise the extended leg, flex the knee and flex the ankle, and was rated per joint (0=no, 1=partial, 2=complete motor block). The results obtained on both extremities were added, giving a maximum score of 12 (complete motor block). The following

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variables were recorded: time to maximum cephalad spread of analgesia; highest level of analgesia; and degree of motor block. The study was observer-blind, that is the investigator assessing the level of analgesia and intensity of motor block was unaware of the site of injection.

Systemic arterial pressure, measured with an automatic cycling device (Accutor 1, Datascope, Helsinki, Finland) and heart rate (from the electrocardiogram) were monitored before injection, during induction, during surgery and in the recovery room at the following times: at 5-min intervals during the first 0.5 h and then at 15-min intervals until the patient was returned to the ward. If systolic arterial pressure decreased more than 30% below the preanaesthetic value or to less than 90 mm Hg, ephedrine 5 mg was given i.v. Bradycardia (heart rate <55 beat min^{-1}) was treated with atropine 0.25 mg i.v.

Group sizes were based on power analysis, which showed that with the variance in the highest level of analgesia observed in patients older than 65 yr in a previous study[2], 15 patients would be required per group to achieve an 80% probability of detecting a difference of two segments between the groups at the 0.05 level of significance. Data are presented as mean (SD), median (95% confidence intervals (CI)) or frequencies, as appropriate. Medians and confidence limits were corrected for the presence of tied observations[6]. Patient characteristics were analysed using the two-tailed, two-sample t test. Neural block characteristics were analysed with the two-tailed Mann–Whitney U test. Fisher's exact test was used for comparison of proportions. Haemodynamic data were examined using a repeated measurements analysis of variance design. Maximum changes in systolic arterial pressures (SAP) and heart rate (HR) were compared between groups using the two-tailed Mann–Whitney U test. $P<0.05$ was considered statistically significant.

Results

The groups were comparable in age, height and weight (table 1). Block characteristics are summarized in table 2 and were comparable between the groups. In all patients symmetrical analgesia levels were obtained. The median highest level of analgesia was T7.0 (CI T4.6–T9) in group 1 and T7.2 (T5.7–T8) in group 2 (fig. 1). Median times to reach the highest level of analgesia were 15.0 (CI 11.7–23.0) min and 16.4 (CI 10.0–19.3) min in groups 1 and 2, respectively. All patients in group 1 and 14 patients in group 2 achieved the maximum degree of motor block (score 12) before the start of surgery.

Analgesia was adequate for surgery in all patients. Changes in SAP and HR were similar in both groups (table 3). Two patients in group 1 and one patient in group 2 required ephedrine for treatment of hypotension. No patient developed post-spinal headache.

Table 1 Patient characteristics (mean (SD or range)). Group 1 = injection at the L3–4 interspace; group 2 = injection at the L4–5 interspace. No significant differences between groups

	Group 1 (n=15)	Group 2 (n=15)
Age (yr)	75 (68–87)	76 (69–82)
Height (cm)	174 (8)	175 (5)
Weight (kg)	73 (11)	76 (10)

Table 2 Neural block characteristics (median (95% CI) or number of patients (%)). Group 1 = injection at the L3–4 interspace; group 2 = injection at the L4–5 interspace. No significant differences between groups

	Group 1 (n=15)	Group 2 (n=15)
Analgesia		
Highest level	T7.0 (T4.6–T9.0)	T7.2 (T5.7–T8.0)
Time to maximal cephalad spread (min)	15 (12–23)	16 (10–19)
Motor block		
Patients with complete block	15 (100)	14 (93)

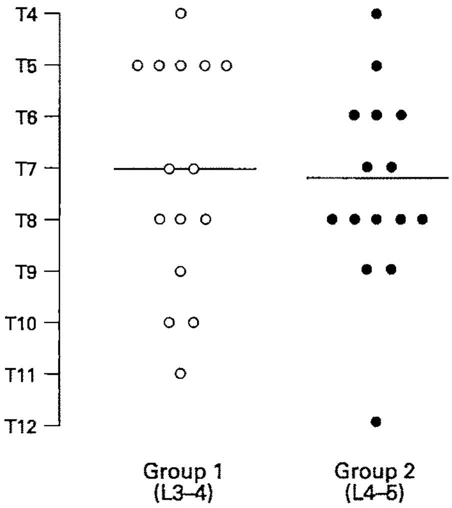

Figure 1 Highest levels of analgesia in individual patients after injection of 0.5% hyperbaric bupivacaine 3 ml at the L3–4 or L4–5 interspace. Horizontal lines=medians (corrected for ties).

Discussion

Several studies have shown that analgesia levels obtained after subarachnoid injection of a hyperbaric local anaesthetic solution are approximately 3–4 spinal segments higher in elderly compared with young adults patients[1–3]. The same presumably holds for levels of sympathetic block that are associated with analgesia levels, but are generally 2–4 segments higher. Consequently, the highest levels of sympathetic block are often in the upper thoracic region in elderly patients, which may explain the higher

Table 3 Haemodynamic data (median (95% CI) or number of patients (%)). Group 1 = injection at the L3–4 interspace; group 2 = injection at the L4–5 interspace. No significant differences between groups

	Group 1 (n=15)	Group 2 (n=15)
Maximum decrease in SAP (%)	23 (15–29)	18 (16–22)
Time to maximum decrease in SAP (min)	30 (18–40)	18 (10–30)
Maximum decrease in HR (%)	11 (6–19)	13 (7–25)
Time to maximum decrease in HR (min)	43 (33–53)	34 (25–49)
Patients requiring ephedrine	2 (13)	1 (7)

frequency of cardiovascular side effects in elderly compared with young adult patients[4,5]. Factors that contribute to the more extensive block in the elderly include gradual degeneration of the central and peripheral nervous system[7,8], changes in the anatomical configuration of the lumbar and thoracic spine[9], and possibly a reduction in the volume of the cerebrospinal fluid[10].

The main objective of this study was to determine if injection of a hyperbaric bupivacaine solution at a lower (L4–5) than usual (L3–4) lumbar interspace reduced cephalad spread of local anaesthetic solution and thereby limited the highest analgesia levels. The study was based on earlier observations which showed that a hyperbaric local anaesthetic solution produced bimodal spread when the patient was turned supine and remained on a horizontal plane after midlumbar (L3–4) subarachnoid injection. In this situation the solution is under the influence of gravity and migrates preferentially to the low levels of the subarachnoid space, that is below L3 in the lumbosacral concavity or above L3 in the thoracic concavity[11]. If, however, the epicentre of the injection lies at L4–5 in the declining portion of the lumbar lordosis, a greater portion of the solution may spread in a caudad direction. The study was encouraged by recent observations of Hirabayashi and colleagues[12] who examined the anatomical configuration of the spinal column in supine volunteers using magnetic resonance imaging (MRI). They demonstrated that the median highest point was not located at L3, as is commonly believed, but at L4 (range L3–4 to L4), explaining partly why a uniform dose of hyperbaric anaesthetic solution shows variable levels of analgesia when injected via either the L3–4 or L4–5 interspace. It should be emphasized, however, that Hirabayashi and colleagues studied younger patients (aged 16–63 yr). In elderly patients, such as in this study, the highest point may have migrated because of degenerative processes.

As it is well known that lumbar interspaces may be easily misidentified[13], identification in this study was made independently by two anaesthetists who counted the spines of the vertebrae from both the cranial and caudad directions and palpated the iliac crest to confirm the position of the fourth lumbar vertebra. Despite these precautions it is possible that misidentification occurred in some patients. More definite identification of the correct interspaces would have required x-ray marking. However, we abstained from such procedures for ethical reasons. Moreover, such identification techniques may invalidate the results for prospective use in routine clinical practice, where these techniques are not used.

The results of this study confirm that there is considerable spread in the highest levels of analgesia when a hyperbaric solution is administered to elderly patients. Furthermore, the results are in keeping with those of two earlier studies from our institute on the influence of age on the quality of neural block after subarachnoid administration of hyperbaric bupivacaine at the L3–4 interspace[2,3]. Median highest levels of analgesia in elderly patients (>65 yr) in those studies were approximately T9 and T7, respectively. The results of this study were, however, disappointing in that injection at the L4–5 interspace did not result in lower analgesia levels compared with injection at the L3–4 interspace, and haemodynamic changes did not differ between groups. The lack of effect of the site of injection on analgesia levels is consistent with the findings of Sundnes and colleagues[14], the only investigators who have reported on the effect of site of injection on analgesia levels attained with hyperbaric bupivacaine, and they observed no correlation between the site of injection (L2–3 or L3–4) and the highest level of analgesia. However, their study was designed primarily to study the effects of volume of injected solution and patients were not allocated randomly to the puncture site.

The effects of varying sites of injection have not been studied as extensively with hyperbaric as with plain bupivacaine solutions. However, with plain solutions there are discrepancies between studies that have examined the influence of different injection sites on analgesic spread[15-18]. There was no significant difference in maximal level of sensory block when plain bupivacaine solutions were injected in elderly patients at different levels, with patients in the sitting position during injection and until 2 min thereafter, when patients were turned supine[15,16]. In contrast, when solutions were injected with the patient in the lateral horizontal position and then turned immediately supine after injection, highest analgesia levels were 4 segments higher when the injection was at the L2–3 interspace compared with the L3–4 or L4–5 interspace[17,18]. Although comparisons between studies may be confounded by differences in the temperature of the injected solutions (room temperature *vs* body temperature), which affects baricity (at room temperature 0.5% plain bupivacaine is usually slightly hyperbaric, at body temperature usually slightly hypobaric, depending on the density of the CSF, which may vary between patients), these observations suggest that the effect of the site of injection is dependent on the positioning of the patient, at least with plain bupivacaine solutions.

References

1. Racle JP, Benkhadra A, Poy JY, Gleizal B. Spinal analgesia with hyperbaric bupivacaine: influence of age. *British Journal of Anaesthesia* 1988; **60**: 508–514.
2. Veering BT, Burm AGL, Spierdijk J. Spinal anaesthesia with hyperbaric bupivacaine: effects of age on neural blockade and pharmacokinetics. *British Journal of Anaesthesia* 1988; **60**: 187–194.
3. Veering BT, Burm AGL, Vletter AA, van den Hoeven RAM, Spierdijk J. The effect of age on systemic absorption and systemic disposition of bupivacaine after subarachnoid administration. *Anesthesiology* 1991; **74**: 250–257.
4. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. *Anesthesiology* 1992; **76**: 906–916.
5. Chamberlain DP, Chamberlain BDL. Changes in the skin temperature of the trunk and their relationship to sympathetic blockade during spinal anesthesia. *Anesthesiology* 1986; **65**: 139–143.
6. Zar JH. *Biostatistical Analysis*, 2nd Edn. Englewood Cliffs, New Jersey: Prentice-Hall Inc., 1984; 20–23.
7. Bromage PR. *Epidural Analgesia*. Philadelphia, Pennsylvania: WB Saunders, 1978; 40–42.
8. Dorfman LJ, Bosley TM. Age-related changes in peripheral and central nerve conduction in human. *Neurology* 1979; **29**: 38–44.
9. Ericksen MF. Aging in lumbar spine. *American Journal of Physical Anthropology* 1978; **48**: 241–246.
10. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesthesia and Analgesia* 1985; **64**: 715–730.

11. Smith TC. The lumbar spine and subarachnoid block. *Anesthesiology* 1968; **29**: 60–64.
12. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H, Furuse M. Anatomical configuration of the spinal column in the supine position. I. A study using magnetic resonance. *British Journal of Anaesthesia* 1995; **75**: 3–5.
13. Moore DC. Guest discussion. *Anesthesia and Analgesia* 1970; **49**: 916–917.
14. Sundnes KO, Vaagenes P, Skretting P, Lind B, Edström HH. Spinal analgesia with hyperbaric bupivacaine: effects of volume of solution. *British Journal of Anaesthesia* 1982; **54**: 69–74.
15. Becker N, Callesen T, Thage B, Bertelsen F, Christiansen C. Level of injection in spinal anesthesia: effect on sensory anesthetic level. *Regional Anesthesia* 1993; **18**: 44–46.
16. Olsen KH, Nielsen TH, Kristoffersen E, Husegaard HC, Wernberg M, Dørup J. Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5. *British Journal of Anaesthesia* 1990; **64**: 170–172.
17. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
18. Tuominen M, Taivainen T, Rosenberg PH. Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection. *British Journal of Anaesthesia* 1989; **62**: 358–361.

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Inflammatory changes after extradural anaesthesia may affect the spread of local anaesthetic within the extradural space

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Summary

We have assessed cephalad spread of analgesia in 491 patients undergoing extradural anaesthesia at the L2–3 or L3–4 interspace. Patients were classified into one of three groups based on the number of previous lumbar extradural anaesthesia procedures: none (group I, *n*=339), one (group II, *n*=82), and two or more (group III, *n*=70). Cephalad spread of analgesia was greater in group I than in groups II and III, regardless of the puncture site. In addition, we examined the extradural space using a flexible extraduroscope in 32 patients who were excluded from the analysis of spread. Extraduroscopy showed the extradural space to be patent in patients with no history of prior lumbar extradural anaesthesia, but it was not clearly identified in patients who had received extradural anaesthesia one or more times because of aseptic inflammatory changes, including proliferation of connective tissue, adhesions between the dura mater and the ligamentum flavum, granulation and changes in the ligamentum flavum. Extradural anaesthesia may cause aseptic inflammatory changes in the extradural space which may reduce the spread of analgesia. (*Br. J. Anaesth.* 1996;**77**:347–351)

Key words

Anaesthetic techniques, extradural. Equipment, extradural space indicators.

Repeat extradural anaesthesia has been reported to be unreliable compared with initial extradural anaesthesia, resulting occasionally in unilateral or failed block [1 2]. However, the reasons for the unreliability of repeat extradural anaesthesia have not been investigated thoroughly. Extraduroscopy provides a clear view of the lumbar extradural space [3 4]. Therefore, we have studied the effects of repeat extradural anaesthesia on the spread of analgesia and on extraduroscopic findings.

Patients and methods

The study was approved by the local Ethics Committee and informed consent was obtained from all patients. Data were obtained from 523 patients who received extradural anaesthesia for a variety of therapeutic or surgical procedures, including extracorporeal shock-wave lithotripsy, transurethral resection of the prostate and transurethral resection of bladder tumours.

In order to estimate the effects of repeated extradural anaesthesia on the spread of analgesia, we assessed cephalad spread of analgesia in 491 patients undergoing lumbar extradural anaesthesia performed at the L2–3 or L3–4 interspace. Patients were classified into one of three groups based on the number of previous lumbar extradural anaesthesia procedures: none (group I, *n*=161 (L2–3), *n*=198 (L3–4)), one (group II, *n*=33 (L2–3), *n*=56 (L3–4)) and two or more (group III, *n*=26 (L2–3), *n*=49 (L3–4)). Patients with a history of prior extradural anaesthesia of the cervical, thoracic or sacral region were excluded. Each patient was premedicated with hydroxyzine 25–50 mg. Patients were then placed in the right lateral decubitus position on a horizontal operating table. A 17-gauge Tuohy needle was introduced at either the L2–3 or L3–4 interspace using the paramedian technique. The extradural space was identified using loss of resistance with a small amount of air. When no cerebrospinal fluid or blood flowed from the needle, 2% mepivacaine 20 ml were injected into the extradural space via the needle over a period of 20 s. An extradural catheter (outside diameter 1 mm; Hakko, Tokyo, Japan) was inserted 5 cm in a cephalad direction into the extradural space, and the patient was placed in the supine position. Fifteen minutes after injection, the cephalad level of analgesia was determined using the pinprick test and referring to a dermatome chart[5] by pre-selecting the dependent side to record. Additional local anaesthetic was administered via the catheter 15 min after the initial injection if the level of analgesia was inadequate for the planned therapeutic or surgical procedure.

In order to evaluate the effects of repeated extradural anaesthesia on the extraduroscopic findings, we examined the lumbar extradural space in the other 32 patients. These patients underwent the

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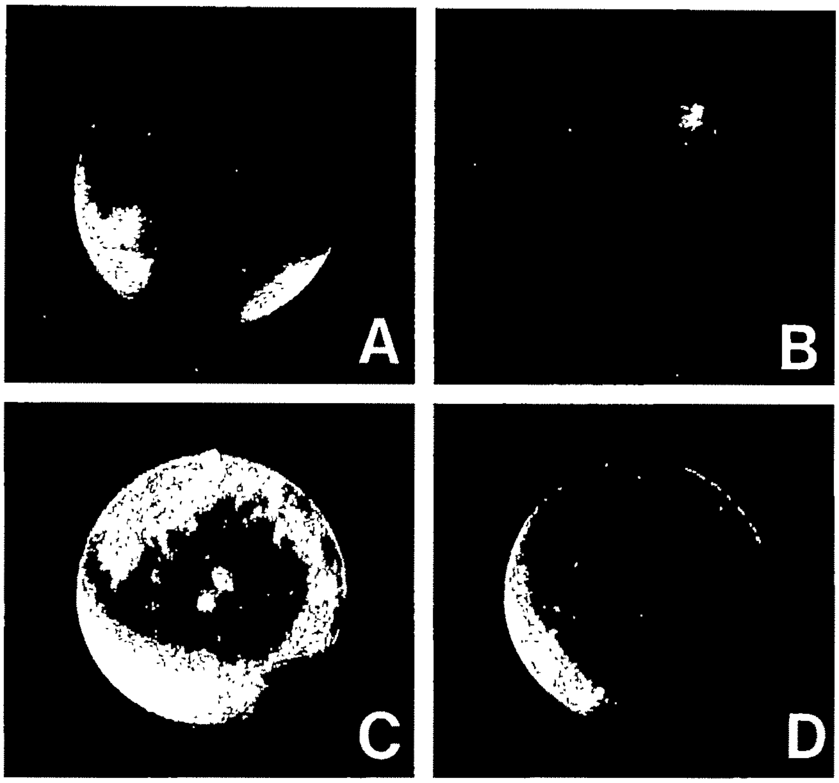

Figure 1 Photographs of the lumbar extradural space obtained by extraduroscopy in patients with no history of prior extradural anaesthesia. The views are cephalad. The extradural space in a 53-yr-old woman is observed as a patent canal (A). The upper part of the canal appears yellow and was identified as the ligamentum flavum. The lower part appears as a white membrane with associated blood vessels and was identified as the dura mater. Bleeding was induced by the introduction of the Tuohy needle in a 51-yr-old man (B). The connective tissue in a 55-yr-old woman was so fragile (C) that the extraduroscope was able to break it easily (D).

same technique of extradural puncture and additional examination of the lumbar extradural space with a flexible fibrescope, either 0.5 or 0.8 mm in diameter (Olympus AF type 5 or type 8, Tokyo, Japan) immediately after identifying the extradural space. The fibrescope was connected to a television monitor system (Olympus OTV-A and CLV-A, Tokyo, Japan) and introduced into the extradural space easily through the Tuohy needle. Patients who underwent extraduroscopy were excluded from analysis of spread.

Statistical analyses were performed with the StatView package version 4.02 (Abacus Concepts, CA, USA) on a Macintosh Quadra 650 (Apple Computer Inc., CA, USA). Age, weight and height are expressed as mean (SD or range), and values were compared using repeated measures analysis of variance after Dunn's procedure. The level of analgesia is expressed as median (range), and values were compared using the Kruskal–Wallis test after Mann–Whitney's *U* test. $P<0.05$ was considered statistically significant.

Results

Age, weight and height did not differ between the three groups of patients undergoing extradural anaesthesia at the L2–3 or L3–4 interspace (tables 1, 2). Cephalad spread of analgesia was greater in group I than in both groups II and III, regardless of the puncture site (tables 1, 2). There were no differences in cephalad spread of analgesia between groups II and III, regardless of the puncture site. Unilateral block was not observed in any of the patients examined.

Figure 1 shows typical photographs obtained via the extraduroscope in patients with no history of prior extradural anaesthesia. The extradural space in a 53-yr-old woman was observed as a patent canal (fig. 1A). The upper part of the canal appeared yellow and was identified as the ligamentum flavum. The lower part appeared as a white membrane with associated blood vessels and was identified as the dura mater. The introduction of the Tuohy needle induced bleeding in a 51-yr-old man (fig. 1B). The connective tissue in a 55-yr-old woman (fig. 1C) was

Table 1 Age, height, weight and cephalad spread of analgesia in patients undergoing extradural anaesthesia at the L2–3 interspace (mean (SD or range)) or (median [range]). $^*P < 0.05$ *vs* group I

	Group I (n=153)	Group II (n=30)	Group III (n=23)
Age (yr)	50 (22–77)	52 (24–75)	54 (25–85)
Height (cm)	161 (8)	162 (7)	161 (8)
Weight (kg)	61 (10)	61 (11)	63 (11)
Cephalad spread	T6 [T2–T11]	T7* [T4–T11]	T8* [T2–T12]

Table 2 Age, height, weight and cephalad spread of analgesia in patients undergoing extradural anaesthesia at the L3–4 interspace (mean (SD or range)) or (median [range]). $^*P < 0.05$ *vs* group I

	Group I (n=186)	Group II (n=52)	Group III (n=47)
Age (yr)	53 (21–84)	57 (28–83)	54 (24–88)
Height (cm)	163 (7)	161 (7)	162 (7)
Weight (kg)	61 (10)	62 (9)	64 (10)
Cephalad spread	T7 [T2–T11]	T8* [T3–T12]	T8* [T4–T12]

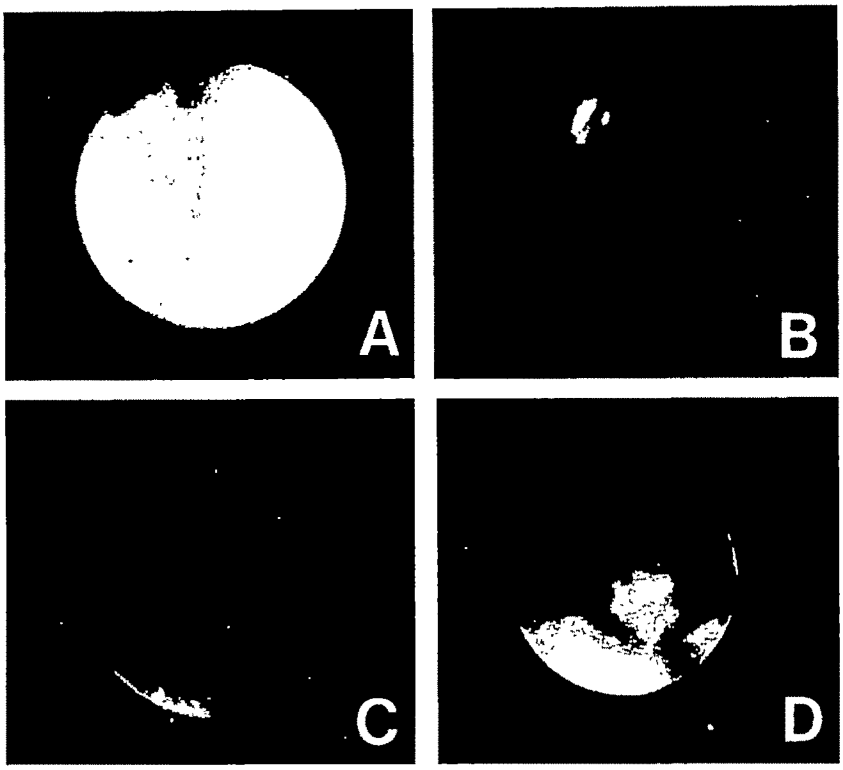

Figure 2 Photographs of patients with a history of previous extradural anaesthesia. Connective tissue has proliferated and the extradural space cannot be identified as a patent canal in a 67-yr-old woman with a history of three prior extradural anaesthesia procedures (A). When the endoscope was withdrawn, a channel was observed (B). Adhesions are seen between the dura mater and the ligamentum flavum in a 72-yr-old man who had undergone extradural anaesthesia 1 month previously (C). Granulation is seen in a 61-yr-old man who underwent extradural anaesthesia 3 months previously (D).

so fragile that the extraduroscope was able to break it easily (fig. 1D).

Figures 2 and 3 show typical photographs in patients with a history of previous extradural anaesthesia. The connective tissue had proliferated and the extradural canal could not be identified clearly in a 67-yr-old woman with a history of three prior extradural anaesthesia procedures (fig. 2A). The contents were a homogeneous fat pad without fibrous septation. It was possible to advance the extraduroscope through this connective tissue without resistance. When the extraduroscope was withdrawn, a channel produced by the scope was observed in the connective tissue (fig. 2B). Other extraduroscopic findings were as follows: adhesion between the dura mater and the ligamentum flavum in a 72-yr-old man who had undergone extradural anaesthesia 1 month previously (fig. 2C), granulation in a 61-yr-old man who had undergone extradural anaesthesia 3 months previously (fig. 2D), irregularities in the ligamentum flavum in a 68-yr-old man who had undergone extradural anaesthesia 1 month previously (fig. 3A) and irregular proliferation of connective tissue and blood vessels in a 64-yr-old man who had undergone extradural anaesthesia six times within a 3-yr period, the most recent 3 months previously (fig. 3B). This proliferation of connective tissue was seen to occlude the extradural space.

We encountered no accidental dural punctures and observed no signs of neurological injury in any of our patients.

Discussion

We have found that cephalad spread of analgesia was reduced in patients with a history of prior lumbar extradural anaesthesia, and extraduroscopic examination revealed significant inflammatory changes occluding the extradural space in these patients. These inflammatory changes may have affected the spread of local anaesthetic within the extradural space. Similar findings were observed in patients who had undergone only one prior extradural anaesthetic procedure, and the spread of analgesia in patients who had received extradural anaesthesia only once was similar to that in patients who had received extradural anaesthesia two or more times.

Repeated extradural anaesthesia has been reported to be unreliable in patients undergoing extracorporeal shock-wave lithotripsy[2]. In our study, we confirmed the reduction in cephalad spread of analgesia in patients undergoing repeated extradural anaesthesia. Why does repeat extradural anaesthesia become unreliable? We suggest that inflammatory changes in the extradural space, resulting from prior extradural anaesthesia, may play an important role in limiting cephalad spread of analgesia. In this study, the inflammatory changes observed included proliferation of connective tissue, adhesions between the dura mater and the ligamentum flavum, and granulation and irregularities in the extradural space. Proliferation of connective tissue, whether homogeneous or irregular, occluding the extradural space may hinder cephalad spread of anaesthetic. Adhesions between the dura mater and the ligamentum flavum may also interfere with spread. Granulation and irregularities in the extradural space may interfere with penetration of anaesthetic into the spinal nerve roots because the anaesthetic is absorbed through the connective tissue.

It should be noted, however, that this reduction in cephalad spread of analgesia was not observed in all patients undergoing repeat extradural anaesthesia.

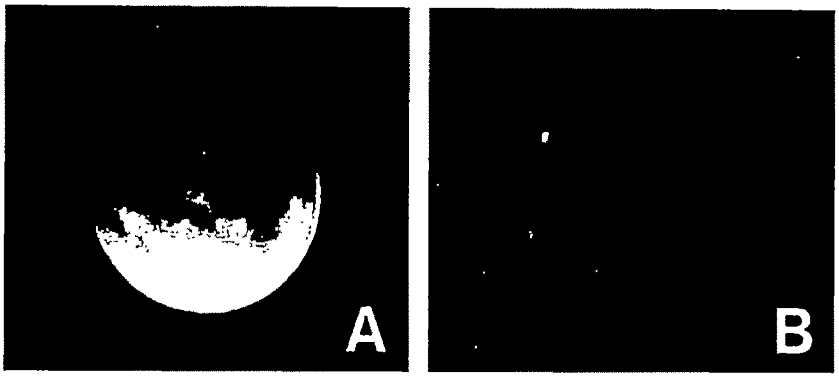

Figure 3 Photographs of patients with a history of prior extradural anaesthesia. Irregularities are seen in the ligamentum flavum in a 68-yr-old man who had undergone extradural anaesthesia 1 month previously (A). Irregular proliferation of connective tissue and blood vessels is observed in a 64-yr-old man who underwent extradural anaesthesia six times in a 3-yr period, the most recent 3 months previously (B).

Wide variations in the level of analgesia were seen in patients who underwent repeat extradural anaesthesia, and these variations were similar to those encountered in initial extradural anaesthesia. Inflammatory changes, including proliferation of connective tissue and adhesions between the dura mater and the ligamentum flavum, may play a role in limiting cephalad spread of anaesthetic. On the other hand, narrowing of the extradural space resulting from these inflammatory changes might be expected to increase cephalad spread of anaesthetic in repeat anaesthesia, as when the same volume of solution is injected into a narrower space, it might spread over a wider area. This may explain the observation that some patients with a history of prior extradural anaesthesia were found to have significant cephalad spread of analgesia. Therefore, the inflammatory changes in the extradural space alone cannot explain the variations in spread observed in patients undergoing repeat extradural anaesthesia. The specific findings observed by extraduroscopy may play an important role in determining the spread of local anaesthetics in extradural anaesthesia.

The absence of any differences in the spread of analgesia between groups II and III is extremely interesting, and suggests that inflammatory changes can be induced by a single extradural anaesthesia procedure. However, the connective tissue after initial extradural anaesthesia differed from that seen after repeat anaesthesia. In the former, the connective tissue was found to be fragile and elastic, whereas in the latter case, it was dense and hard. When the extraduroscope was withdrawn, these differences were immediately obvious. The connective tissue was more easily broken in the former than in the latter. In our patients, prior extradural anaesthesia always involved introduction of a Tuohy needle and a catheter, followed by administration of local anaesthetic. Inflammatory changes induced by the introduction of an extradural catheter have been demonstrated in both animals[6 7] and humans[8 9]. Administration of local anaesthetic alone may also cause inflammation[6-10]. In addition, bleeding induced by the introduction of the Tuohy needle was observed frequently in extraduroscopic examinations. The factors responsible for the inflammatory changes in the extradural space are unclear.

In assessing the results of this study, we should also consider the fact that the extradural space was observed after introducing a small amount of air. The extradural space is sometimes described as a potential space, rather than a true cavity[11 12]. The introduction of air may therefore have affected our extraduroscopic findings, expanding the extradural space and stretching the connective tissues. However, in our study, all patients received identical extradural punctures, and the effects of the air introduced into the extradural space should have been similar in all cases. Therefore, we believe that this factor had no influence on our comparative findings. In addition, patients who underwent extraduroscopy were excluded from the analysis of spread, because extraduroscopy made channels in the extradural space and broke down the adhesions, thereby altering the spread of drug in the extradural space.

The incidence of unilateral block after administration of local anaesthetic via a catheter has been reported to be higher in repeat block than in initial block[1]. In this study, we observed no unilateral block after administration of local anaesthetic via the needle. The laterality of the block may occur after administration of local anaesthetic via a catheter, presumably because of the misplaced catheter into the lateral side in the extradural space by aseptic inflammatory changes. Further observations are required.

In summary, extradural anaesthesia caused inflammatory changes characterized by proliferation of connective tissue, adhesions and granulation, and irregularities in the extradural space. These inflammatory changes may affect the distribution of local anaesthetic within the extradural space.

References

1. Withington DE, Weeks SK. Repeat extradural analgesia and unilateral block. *Canadian Journal of Anaesthesia* 1994; **41**: 568–571.
2. Korbon GA, Lynch C III, Arnold WP, Ross WT, Hudson SB. Repeated extradural anaesthesia for extracorporeal shock-wave lithotripsy is unreliable. *Anesthesia and Analgesia* 1987; **66**: 669–672.
3. Blomberg RG, Osson SS. The lumbar extradural space in patients examined with epiduroscopy. *Anesthesia and Analgesia* 1989; **68**: 157–160.
4. Blomberg R. The dorsomedian connective tissue band in the lumbar extradural space of humans: An anatomical study using epiduroscopy in autopsy cases. *Anesthesia and Analgesia* 1986; **65**: 747–752.
5. Cousins MJ, Bromage PR. Extradural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade. Clinical*

Anesthesia and Management of Pain, 2nd Edn. Philadelphia: JB Lippincott, 1988; 344.

6. Kyttä J, Rosenberg PH, Wahlstöm TR. Effects of continuous extradural administration of bupivacaine through a catheter in pigs. *European Journal of Anaesthesiology* 1986; **3**: 473–480.
7. Larsen JJ, Svendsen O, Andersen HB. Microscopic extradural lesion in goats given repeated extradural injections of morphine: Use of a modified autopsy procedure. *Acta Pharmacologica et Toxicologica* 1986; **58**: 5–10.
8. Brasseur L, Boura J, Brunet A-M, Gabriel P, Begon L, Descorps-Declere A. Failure of long-term extradural catheters. *Anaesthesia* 1987; **42**: 557.
9. Brems-Dalgaard E, Just SL, Pedersen H. Encapsulated extradural catheter: CT findings. *Neuroradiology* 1991; **33**: 81–82.
10. Steiness E, Rasmussen F, Svendsen O, Nielsen P. A comparative study of serum creatine phosphokinase (CPK) activity in rabbits, pigs and humans after intramuscular injection of local damaging drugs. *Acta Pharmacologica et Toxicologica* 1978; **42**: 357–364.
11. Parkin IG, Harrison GR. The topographical anatomy of the lumbar extradural space. *Journal of Anatomy* 1985; **141**: 211–217.
12. Harrison GR. The extradural space. *Anaesthesia* 1989; **44**: 361–362.

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Acid–base state of cerebrospinal fluid during pregnancy and its effect on spread of spinal anaesthesia

Y. Hirabayashi, R. Shimizu, K. Saitoh, H. Fukuda and T. Igarashi

Summary

To assess the possible relationship between changes in acid–base state of cerebrospinal fluid (CSF) and enhanced spread of spinal anaesthesia during pregnancy, we have measured CSF pH, carbon dioxide tension ($P\text{co}_2$) and HCO_3^- values in 73 women undergoing spinal anaesthesia with hyperbaric amethocaine 8 mg. Patients were allocated to one of four groups according to gestational period: non-pregnant group (n=13), first trimester group (8–13 weeks, n=19), second trimester group (14–26 weeks, n=11) and third trimester group (27–39 weeks, n=30). The pH of the CSF was greater in the second and third trimester groups than in the non-pregnant group. CSF $P\text{co}_2$ decreased by 0.53–0.8 kPa throughout pregnancy. CSF HCO_3^- was decreased throughout pregnancy. Overall, no clinically significant correlation was found between maximum cephalad spread of analgesia and CSF pH, $P\text{co}_2$ or HCO_3^-. We conclude that pregnancy-induced changes in acid–base state of CSF have little effect on the spread of spinal anaesthesia, although there is a clinically different spread of spinal anaesthesia between non-pregnant and pregnant states. (*Br. J. Anaesth.* 1996;**77**:352–355)

Key words

Anaesthetic techniques, subarachnoid. Anaesthesia, obstetric. Acid–base equibrium, pH. Anaesthetics local, amethocaine. Cerebrospinal fluid. Pregnancy.

The spread of regional anaesthesia is reported to be enhanced in pregnant compared with non-pregnant women[1–5]. Mechanical[6–8] and hormonal[9–11] changes have been implicated as possible factors for pregnancy-induced enhancement of regional anaesthesia. In addition, acid–base changes during pregnancy have been suggested to affect spread of extradural anaesthesia[5].

Cerebrospinal fluid (CSF) is in contact with the spinal cord and spinal nerve roots, and changes in acid–base state of CSF during pregnancy may therefore affect spread of spinal anaesthesia. Although many investigators reported acid–base state of arterial blood during pregnancy[12–16], there are few studies which have dealt with acid–base state of CSF in pregnant women. The purpose of this study was to see if changes in acid–base state of CSF correlated with enhanced spread of spinal anaesthesia during pregnancy.

Patients and methods

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients. We studied 13 non-pregnant and 60 pregnant women. All patients, ASA I–II, had no major health problems and no contraindications to spinal anaesthesia. Patients were allocated to one of four groups according to gestational period: non-pregnant group (n=13), first trimester group (8–13 weeks, n=19), second trimester group (14–26 weeks, n=11) and third trimester group (27–39 weeks, n=30). Operative procedures included arthroscopic operation on the knee (n=13) in the non-pregnant group; procedures for cervical incompetency in the first (n=19) and second (n=11) trimester groups; and procedures for cervical incompetency (n=6) and Caesarean section (n=24) in the third trimester group.

None of the patients was premedicated. Patients were placed in the lateral position on a horizontal operating table. Under aseptic conditions, lumbar puncture was performed at the L3–4 interspace with a 25-gauge Quincke needle using a median approach. The needle was inserted with its bevel orientated parallel to the dural fibres and then rotated 90° to direct the bevel cephalad. To determine acid–base state of CSF, 1 ml of CSF was withdrawn just before administration of the drug. CSF pH, carbon dioxide tension ($P\text{co}_2$) and HCO_3^- were measured using a blood-gas analyser (178 pH/blood gas analyser, Ciba Corning Diagnostics, Boston, MA, USA) within 5 min. Amethocaine 8 mg in 2 ml of 10% glucose was given over 40 s. Lumbar puncture and sampling were performed by one anaesthetist who was unaware of the patient's group assignment, although he knew the type of surgery and abdominal girth. Immediately after spinal injection, patients were turned gently to the supine horizontal position. No attempt was made to influence the level of sensory block by manipulating the operating table. Patients undergoing procedures for cervical incompetency were placed gently in the horizontal lithotomy position, 30 min after spinal injection. Left uterine displacement was applied

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to parturients undergoing Caesarean section until the beginning of the operation. A second anaesthetist who was blinded to the CSF data assessed the spread of analgesia bilaterally using pinprick at 5, 10, 15, 20, 30 and 60 min after spinal injection according to a dermatomal chart. If the analgesic level differed on each side, the average value was used for analysis. In 22 of the 73 patients, an aliquot of the CSF sample was provided for progesterone analysis, which has been reported previously[11].

Comparisons between the four groups were made by analysis of variance (ANOVA) followed by Fisher's protected least significant difference test for parametric data, and Kruskal–Wallis followed by Mann–Whitney *U* test for non-parametric data. Correlation between indices of acid–base state and maximum cephalad spread of analgesia was analysed using Spearman's rank correlation coefficient (ρ). $P<0.05$ was considered significant.

Results

There were no differences in age and height between the four groups (table 1). Median gestational age indicated that patient characteristics in the first trimester group clustered at the end of the range, second trimester group at the beginning of the range and third trimester group at the end of the range. The characteristics of the third trimester patients were similar gestationally to term parturients. Maximum cephalad spread of analgesia was higher in the second and third trimester groups than in the non-pregnant group. Times to maximum cephalad spread did not differ between the four groups (table 2).

CSF pH was greater in the second and third trimester groups than in the non-pregnant group (table 3). CSF pH did not correlate with maximum cephalad spread of analgesia (fig. 1A). CSF $P\mathrm{co}_2$ was decreased by 0.53–0.8 kPa below non-pregnant levels even during the early stages of pregnancy and was maintained at this decreased level for the remainder of the pregnancy (table 3). CSF $P\mathrm{co}_2$ correlated inversely with maximum cephalad spread of analgesia (fig. 1B). CSF $\mathrm{HCO_3}^-$ was decreased throughout pregnancy (table 3). CSF $\mathrm{HCO_3}^-$ correlated inversely with maximum cephalad spread of analgesia (fig.1C). Overall, although there were significant differences in the changes in CSF pH, $P\mathrm{co}_2$ and $\mathrm{HCO_3}^-$, changes in median values and ranges were such that these were unlikely to be clinically significant.

Table 1 Patient characteristics (median [range] or mean (SD) [range]) in the non-pregnant, first trimester, second trimester and third trimester (term) pregnant groups. $^*P < 0.05$ *vs* non-pregnant group

	Non-pregnant	First trimester	Second trimester	Third trimester
n	13	19	11	30
Gestational age (weeks)		12 [8–13]	16 [14–26]	37 [28–39]
Age (yr)	34 [21–47]	30 [24–39]	29 [20–34]	30 [22–41]
Height (cm)	156 (8) [140–169]	158 (3) [153–162]	158 (6) [148–168]	156 (6) [144–172]
Weight (kg)	53 (9) [40–75]	55 (6) [44–65]	55 (5) [47–64]	61 (7)* [46–73]

Table 2 Maximum cephalad spread of analgesia and times from spinal injection to maximum spread in the non-pregnant, first trimester, second trimester and third trimester (term) pregnant groups (median [range] or mean (SD)). $^*P < 0.05$; $^{***}P < 0.001$ *vs* non-pregnant group

	Non-pregnant	First trimester	Second trimester	Third trimester
Maximum cephalad spread of analgesia	T6 [T10–T4]	T5 [T11–T2]	T4* [T7.5–T2]	T3.5*** [T5–T2]
Time to maximum spread (min)	21 (8)	18 (7)	21 (8)	19 (8)

Discussion

We have shown that CSF $P\mathrm{co}_2$ began to decrease even in the early stages of pregnancy, and that CSF pH was unchanged during the early stages of pregnancy and then increased for the remainder of the pregnancy. These observations, however, are not surprising. Pregnancy induces an increase in minute ventilation to approximately 50% above non-pregnant levels[6]. This increase in minute ventilation, beginning early in the first trimester, decreases maternal Pa_{CO_2} from 5.33 kPa to approximately 4.0 kPa[12–14 16]. Arterial pH, however, remains near normal because of increased renal excretion of $\mathrm{HCO_3}^-$ [12–14]. The decrease in CSF $P\mathrm{co}_2$ and $\mathrm{HCO_3}^-$ may be a direct result of changing Pa_{CO_2} and lower $\mathrm{HCO_3}^-$ levels in arterial blood. Unlike arterial blood, increased CSF pH during the middle and later stages of pregnancy, observed in this study, suggests a partially compensated acid–base change from non-pregnant controls.

Local anaesthetic solution applied to a nerve membrane exits in two forms: the non-ionized base and the ionized cation[17]. The Henderson–Hasselbalch equation for the equilibrium determines the levels of ionized and non-ionized forms. An increase in pH increases the amount of local anaesthetic in the non-ionized base form, which should enhance the rate of diffusion across the nerve sheath and nerve membrane, resulting in a more rapid onset time of nerve block. In this study, CSF

Table 3 CSF pH, $P\mathrm{co}_2$ and $\mathrm{HCO_3}^-$ (median [range]) in the non-pregnant, first trimester, second trimester and third trimester (term) pregnant groups. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P$ 0.001 *vs* non-pregnant group

	Non-pregnant	First trimester	Second trimester	Third trimester
pH	7.30 [7.27–7.34]	7.31 [7.26–7.35]	7.34* [7.28–7.42]	7.33*** [7.24–7.37]
$P\mathrm{co}_2$ (kPa)	6.30 [5.52–7.10]	5.63*** [4.65–6.19]	5.45*** [4.81–6.20]	5.47*** [4.48–7.36]
$\mathrm{HCO_3}^-$ (mmol litre^{-1})	23.3 [19.6–25.5]	21.5** [18.6–24.1]	21.8* [18.6–23.7]	21.5** [17.3–25.4]

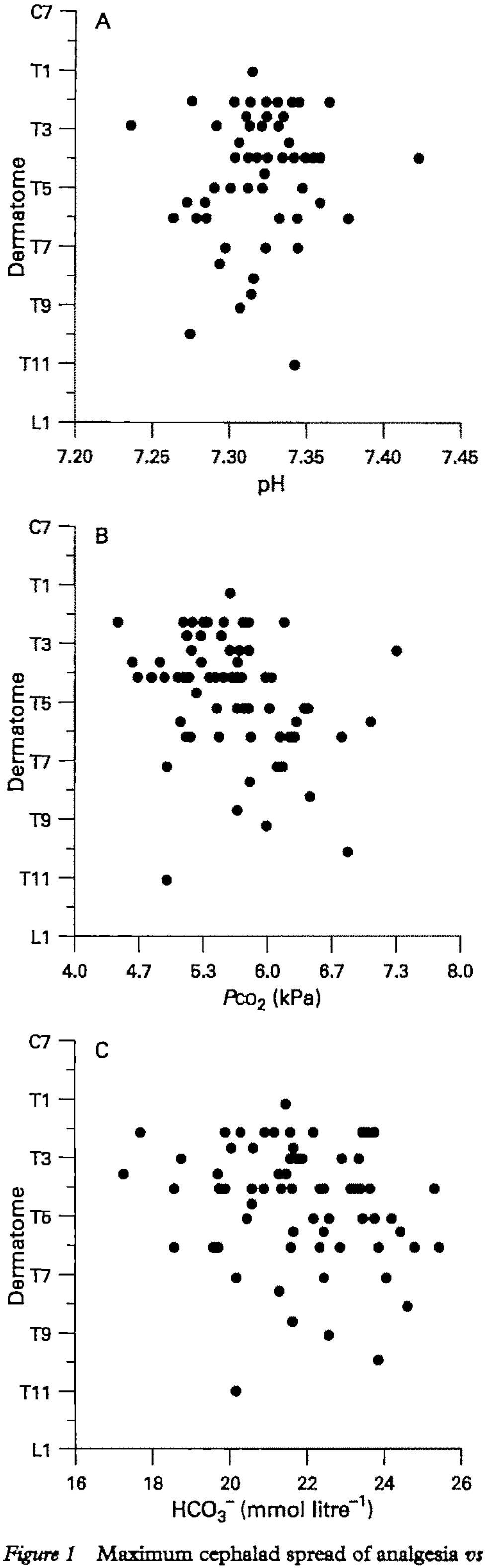

Figure 1 Maximum cephalad spread of analgesia *vs* CSF pH (A), Pco$_2$ (B) and HCO$_3^-$ (C). CSF pH did not correlate with maximum cephalad spread of analgesia (ρ=0.19, P=0.1). CSF Pco$_2$ correlated inversely with maximum cephalad spread of analgesia (ρ=−0.32, P<0.01). CSF HCO$_3^-$ correlated inversely with maximum cephalad spread of analgesia (ρ=−0.24, P<0.05).

pH was greater in the second and third trimester groups than in the non-pregnant group; maximum cephalad spread of analgesia was higher in the former than in the latter group. The increase in CSF pH may, in part, contribute to the observed enhancement of analgesia in the middle and late stages of pregnancy. However, the spinal cord and spinal nerve roots within the dural sac are not covered with sheaths, and thus diffusional delays may have little significance on local anaesthetic action when given directly into the CSF. In this study, CSF pH did not correlate with maximum cephalad spread of analgesia, and times to maximum cephalad spread did not differ between groups. To what degree the change in CSF pH contributed to the observed enhancement of analgesia in the middle and late stages of pregnancy could not be determined.

The presence of carbon dioxide has been reported to enhance both rate and potency of local anaesthetic action[17–21]. This effect is consistent with the ionized cationic form of local anaesthetics being the more active form. After penetration of the nerve sheath and nerve membrane, the non-ionized drug dissociates into the non-ionized base and the ionized cation. The quantity of each varies with the pH of the axoplasm. Carbon dioxide diffuses rapidly across the membrane and causes lowering of intracellular pH. A lowered pH increases the amount of local anaesthetic in the ionized cationic form, which should act as a potent blocker of sodium channels. The results of this study, however, demonstrated that CSF Pco$_2$ correlated inversely with maximum cephalad spread of analgesia. The reason for this inverse correlation is unclear. We speculate that enhancement caused by factors other than carbon dioxide may overshadow the effects of carbon dioxide[6–11].

A decreased buffering capacity during pregnancy has been suggested to explain enhanced extradural anaesthesia during the first trimester of pregnancy[5]. The decreased buffering capacity may allow the local anaesthetic to remain in a salt form for longer and, therefore, stay longer in the area of injection (extradural space). In this study, CSF HCO$_3^-$ was found to decrease during pregnancy. The degree of the decrease, however, was small, and hence local anaesthetics injected directly into the CSF might not be affected significantly. In addition, in accordance with the results of a previous study[4], we failed to demonstrate enhancement of spinal anaesthesia during the first trimester. Unlike extradural anaesthesia[5], spinal anaesthesia during the first trimester may not be affected by pregnancy-induced decreases in buffering capacity.

In contrast with spinal anaesthesia, alkalinization of local anaesthetics has been investigated in extradural anaesthesia. The investigators disagree about the efficacy of this preparation. Some authors reported faster onset and better quality of sensory and motor blocks[22–24]. Others have failed to show any clinical advantages of alkalinization over a plain solution[25–29]. Additional studies are needed to draw definitive conclusions on the onset of extradural anaesthesia with pH-adjusted local anaesthetics.

We showed higher levels of analgesia in pregnant women during the second and third trimesters compared with non-pregnant controls, but did not assess the onset of the block. Therefore, we could not draw any conclusions on the onset of block during pregnancy. However, it is believed that, as a rule, onset of spinal anaesthesia is more rapid during pregnancy. Pregnancy-induced changes, including curvature of the spinal column[7], soft-tissue anatomy within the spinal canal[6 8] and higher progesterone concentrations[11 30], have been implicated as possible factors for the enhancement.

A limitation of this study was the position of the patients examined. This study was performed in clinical patients undergoing various types of operation, but not in volunteers who can be kept in a uniform position throughout the observation. Patients undergoing procedures for cervical incompetency were placed in the horizontal lithotomy position, which is thought to decrease the height of spinal block[31]. However, the horizontal lithotomy position has been reported to have little effect on the height of the block[32 33]. In addition, left uterine displacement was performed in patients undergoing Caesarean section. It could be argued that this manoeuvre might alter the spread of the block but the counter argument would be that in the interest of neonatal well being, the manoeuvre was the best compromise.

References

1. Assali NS, Prystowsky H. Studies on autonomic blockade. I. Comparison between the effects of TEAC and high selective spinal anesthesia on arterial pressure of normal and toxemic pregnancy. *Journal of Clinical Investigation* 1950; **29**: 1354–1366.
2. Barclay DL, Renegar OJ, Nelson EW. The influence of inferior vena cava compression on the level of spinal anesthesia. *American Journal of Obstetrics and Gynecology* 1968; **101**: 792–800.
3. Bromage PR. Continuous lumbar extradural analgesia for obstetrics. *Canadian Medical Association Journal* 1961; **85**: 1136–1140.
4. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Spread of subarachnoid hyperbaric amethocaine in pregnant women. *British Journal of Anaesthesia* 1995; 74: 384–386.
5. Fagraeus L, Urban BJ, Bromage PR. Spread of extradural analgesia in early pregnancy. *Anesthesiology* 1983; **58**: 184–186.
6. Bonica JJ. Maternal anatomic and physiologic alterations during pregnancy and parturition. In: Bonica JJ, McDonald JS, eds. *Principles and Practice of Obstetric Analgesia and Anesthesia*, 2nd Edn. Baltimore: Williams & Wilkins, 1995; 45–79.
7. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Furuse M. Anatomical configuration of the spinal column in the supine position. II. Comparison of pregnant and non-pregnant women. *British Journal of Anaesthesia* 1995; 75: 6–8.
8. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft-tissue anatomy within the vertebral canal in pregnant women. *British Journal of Anaesthesia* 1996; 77: 153–156.
9. Butterworth JF, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology* 1990; 72: 962–965.
10. Datta S, Hurley RJ, Naulty JS, Stern P, Lambert DH, Concepcion M, Tulchinsky D, Weiss JB, Ostheimer GW. Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women. *Anesthesia and Analgesia* 1986; 65: 950–954.
11. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Cerebrospinal fluid progesterone in pregnant women. *British Journal of Anaesthesia* 1995; 75: 683–687.
12. Andersen GJ, James GB, Mathers NP, Smith EL, Walker J. The maternal oxygen tension and acid–base status during pregnancy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1969; 76: 16–19.
13. Dayal P, Murata Y, Takamura H. Antepartum and postpartum acid–base changes in maternal blood in normal and complicated pregnancies. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1972; 79: 612–624.
14. Lucius H, Gahlenbeck H, Kleine H-O, Fabel H, Bartels H. Respiratory functions, buffer system, and electrolyte concentrations of blood during human pregnancy. *Respiration Physiology* 1970; **9**: 311–317.
15. MacRae DJ, Palavradji D. Maternal acid–base changes in pregnancy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1967; **74**: 11–16.
16. Templeton A, Kelman GR. Maternal blood-gases ($P_{A_{O_2}}-P_{a_{O_2}}$), physiological shunt and V_D/V_T in normal pregnancy. *British Journal of Anaesthesia* 1976; **48**: 1001–1004.
17. De Jong RH. *Local Anesthetics*. St Louis: Mosby, 1994
18. Wong K, Strichartz GR, Raymond SA. On the mechanisms of potentiation of local anesthetics by bicarbonate buffer: Drug structure–activity studies on isolated peripheral nerve. *Anesthesia and Analgesia* 1993; **76**: 131–143.
19. Condouris GA, Shakalis A. Potentiation of the nerve-depressant effect of local anaesthetics by carbon dioxide. *Nature (London)* 1964; **204**: 57–59.
20. Catchlove RFH. The influence of CO_2 and pH on local anesthetic action. *Journal of Pharmacology and Experimental Therapeutics* 1972; **181**: 298–309.
21. Bokesch PM, Raymond SA, Strichartz GR. Dependence of lidocaine potency on pH and P_{CO_2}. *Anesthesia and Analgesia* 1987; **66**: 9–17.
22. McMorland GH, Douglas MJ, Jeffery WK, Ross PLE, Axelson JE, Kim JHK, Gambling DR, Robertson K. Effect of pH-adjustment of bupivacaine on onset and duration of extradural analgesia in parturients. *Canadian Anaesthetists Society Journal* 1986; **33**: 537–541.
23. McMorland GH, Douglas MJ, Axelson JE, Kim JHK, Blair I, Ross PLE, Gambling DR, Swenerton JE. The effect of pH-adjustment of bupivacaine on onset and duration of extradural anaesthesia for Caesarean section. *Canadian Journal of Anaesthesia* 1988; **35**: 457–461.
24. DiFazio CA, Carron H, Grosslight KR, Moscicki JC, Bolding WR, Johns RA. Comparison of pH-adjusted lidocaine solutions for extradural anesthesia. *Anesthesia and Analgesia* 1986; **65**: 760–764.
25. Liepert DJ, Douglas MJ, McMorland GH, Gambling DR, Kim JHK, Ross PLE. Comparison of lidocaine CO_2, two per cent lidocaine hydrochloride and pH adjusted lidocaine for Caesarean section anaesthesia. *Canadian Journal of Anaesthesia* 1990; **37**: 333–336.
26. Verborgh C, Claeys M-A, Camu F. Onset of extradural blockade after plain or alkalinized 0.5% bupivacaine. *Anesthesia and Analgesia* 1991; 73: 401–404.
27. Gaggero G, Meyer O, Gessel EV, Rifat K. Alkalinization of lidocaine 2% does not influence the quality of extradural anaesthesia for elective Caesarean section. *Canadian Journal of Anaesthesia* 1995; 42: 1080–1084.
28. Stevens RA, Chester WL, Grueter JA, Schubert A, Brabdon D, Clayton B, Spitzer L. The effect of pH adjustment of 0.5% bupivacaine on the latency of extradural anesthesia. *Regional Anesthesia* 1989; 14: 236–239.
29. Benhamou D, Labaille T, Bonhomme L, Perrachon N. Alkalinization of extradural 0.5% bupivacaine for cesarean section. *Regional Anesthesia* 1989; 14: 240–243.
30. Datta S, Hurley RJ, Naulty JS, Stern P, Lambert DH, Concepcion M, Tulchinsky D, Weiss JB, Ostheimer GW. Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women. *Anesthesia and Analgesia* 1986; 65: 950–954.
31. Smith TC. The lumbar spine and subarachnoid block. *Anesthesiology* 1969; 29: 60–64.
32. Logan MR, Drummond GB. Spinal anesthesia and lumbar lordosis. *Anesthesia and Analgesia* 1988; 67: 338–341
33. Schmidt KA, Snyder SA. Effect of horizontal position on hyperbaric tetracaine spinal anesthesia. *Anesthesia and Analgesia* 1988; 67: 894–896.

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Nausea and vomiting after cardiac surgery

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Summary

We have undertaken a prospective, randomized study to determine the incidence of postoperative nausea and vomiting during intensive care stay after cardiac surgery, and to study the effect of addition of droperidol to an infusion of morphine used for postoperative analgesia. Data from 398 patients were examined. The use of droperidol reduced complaints of nausea from 92 of 198 (46.5%) to 46 of 200 (23%) and episodes of retching or vomiting from 73 of 198 (36.9%) to 44 of 200 (22%). The number of patients requiring rescue antiemetic medication was also reduced significantly from 100 of 198 (50.5%) of those who did not receive droperidol to 44 of 200 (22%) of those given droperidol. Mean duration of intubation was 4.9 h and was unaffected by the use of droperidol. Droperidol had no effect on mean length of stay in the recovery unit. (*Br. J. Anaesth.* 1996;**77**:356–359)

Key words

Vomiting, nausea. Vomiting, nausea, surgical factors. Vomiting, incidence. Surgery, cardiovascular.

Nausea and vomiting are common and distressing symptoms during recovery from anaesthesia and surgery. Studies of postoperative nausea and vomiting (PONV) have concentrated frequently on women undergoing gynaecological procedures and there is little information on the incidence or management of nausea and vomiting after cardiac surgery.

The aim of this study was to assess the incidence of nausea and vomiting in the first 24 h after cardiac surgery, in a unit in which early tracheal extubation is usual[1]. In addition, we wished to ascertain if the addition of droperidol to a continuous infusion of morphine would reduce nausea and vomiting without causing excessive sedation and thereby increase the duration of tracheal intubation and postoperative mechanical ventilation.

Patients and methods

After obtaining approval from the hospital Ethics Committee, we collected data on 442 patients undergoing elective or urgent open heart surgery. Premedication with papaveretum or morphine (10–20 mg) together with hyoscine 0.2–0.4 mg was given i.m. approximately 1 h before surgery. All patients received supplementary oxygen from the time of premedication. After insertion of i.v. and arterial cannulae, anaesthesia was induced with fentanyl 10–15 $\mu g\ kg^{-1}$ and etomidate 5–10 mg. Neuromuscular block was produced with pancuronium and, after tracheal intubation, anaesthesia was maintained with halothane in oxygen and air until the start of cardiopulmonary bypass. Ventilation was adjusted to produce normocapnia. Anaesthesia during bypass was provided by continuous infusion of propofol 6 $mg\ kg^{-1}\ h^{-1}$ and after bypass by halothane in oxygen and air. At the end of surgery, neuromuscular block was antagonized with neostigmine and glycopyrronium and the patient transferred to the cardiac recovery unit (CRU).

After age and sex stratification, patients were allocated randomly to one of two groups: group A received an infusion of morphine 60 mg in saline 58 ml to which was added droperidol 10 mg; group B received a similar infusion of morphine to which 2 ml of normal saline were added. Both patients and nurses caring for them were unaware of the nature of the additive.

After reconnection of monitoring cannulae and initial stabilization in the CRU, the infusion of morphine was commenced. Patients with a body weight greater than 60 kg received an initial bolus dose of morphine 4 mg followed by an initial infusion of 2 $mg\ h^{-1}$, with boluses of 2 mg as indicated. Patients weighing less than 60 kg received an initial dose of 2 mg with an infusion of 1 $mg\ h^{-1}$ and a bolus of 1 mg. The infusion rate was adjusted at the discretion of the attending nurse. If analgesia was inadequate diclofenac 50–100 mg, by suppository, was given, provided there were no contraindications to its use. Patients' lungs were ventilated mechanically until the following criteria for a trial of spontaneous respiration and extubation were met:

1. stable cardiovascular system with an adequate cardiac output. The need for cardiovascular support with inotropic drugs or intra-aortic balloon pump was not a contraindication to extubation provided that haemodynamic state was stable or improving;
2. core temperature > 36 °C;
3. adequate gas exchange with Pa_{O_2} >10 kPa with FI_{O_2} of 50% or less; and
4. no excessive mediastinal bleeding.

The trachea was extubated if the patient was rousable and breathing was clinically adequate, with a ventilatory frequency <30 bpm and oxygen saturation >90% with FI_{O_2}<0.6. Mild hypercapnia ($P\text{CO}_2$

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up to 7.5 kPa) was not a contraindication to extubation. After tracheal extubation patients were seated upright and allowed to breathe oxygen-enriched air.

If the patient did not meet the criteria for tracheal extubation and required sedation to tolerate intubation and ventilation, an infusion of propofol 1–4 mg kg^{-1} h^{-1} was commenced until another trial of spontaneous breathing was performed at the discretion of the nursing staff.

Data collected included patient age, sex, height, weight and operation. When patients were awake, the presence of nausea was ascertained by hourly questioning. Retching or vomiting and need for other antiemetics were noted. As retching is similar to vomiting in all aspects except the production of vomitus, we elected to examine both retching and vomiting together. A "vomiter" was thus any patient who had at least one episode of retching or vomiting. Rescue medication of metoclopramide 10 mg, by slow i.v. injection, was prescribed for all patients and given as required by the nurse caring for the patient. Observations were continued until patients were discharged to the ward on the following day. Duration of intubation, total cumulative dose of morphine administered in the recovery unit, and duration of stay within the recovery area were also noted.

Data were analysed using an unpaired *t* test for patient data and chi-square analysis for comparison of events between groups. $P<0.05$ was considered significant.

Results

Complete data were collected for 398 patients. Data were discarded from 21 patients who had a second anaesthetic for repeat sternotomy or died in the recovery unit, or whose trachea remained intubated for the whole of the first 24 h, and from 20 patients for whom data were incomplete. Data from three other patients who were receiving dialysis for chronic renal failure were also discarded. Age, body weight and sex distribution are shown in table 1. There were no significant differences between the two groups. Operative details are shown in table 2 and were similar for the two groups.

Mean stay in the CRU and therefore number of hours recorded was 21.9 h and was not significantly different between the two groups. Mean morphine consumption during this time was 29 (SD 11.3) mg, with maximum consumption of 60 mg and minimum consumption of 6 mg. There was no correlation between body mass index (weight (kg)/height $(m)^2$) and morphine consumption, or between age and morphine consumption. Mean duration of intubation was 4.9 (4.3) h and was not significantly different between the two groups (table 3).

Table 1 Patient characteristics (mean (range) or number)

	Group A (morphine + droperidol) (*n*= 200)	Group B (morphine + saline) (*n*= 198)
Age (yr)	62.2 (41–85)	62.3 (30–87)
Age of males (yr)	61.7	62.3
Age of females (yr)	63.7	62.4
Sex (M:F)	151:49	139:59
Body weight (kg)	76.9	75.3

Table 2 Details of operations. CAG = Coronary artery graft, AVR = aortic valve replacement

Operation	Group A (morphine + droperidol) (*n* = 200)	Group B (morphine + saline) (*n* = 198)
CAG or repeat CAG	144	137
AVR/AVR repeat	25	23
Other valve	15	15
Valve + CAG	9	11
Other	7	12

Table 3 Postoperative details (mean (SD) or number)

	Group A (morphine + droperidol) (*n* = 200)	Group B (morphine + saline) (*n* = 198)
Duration of intubation (h)	4.8 (4.4)	4.9 (4.3)
Length of stay in recovery unit (h)	21.9 (3.0)	21.8 (4.0)
Total morphine consumption (mg)	28.6 (11.3)	29.4 (11.4)
No. of patients suffering episodes of nausea	46	92
No. of patients with retching or vomiting	37	73
No. of patients requiring rescue medication	44	100

Table 4 Effect of sex on the incidence of postoperative nausea and vomiting

	Males (*n* = 290)	Females (*n* = 108)
No. affected by nausea	84 (29%)	54 (50%)
No. affected by retching or vomiting	66 (23%)	44 (41%)

Table 5 Effect of age on the incidence of postoperative nausea and vomiting

	Age (yr)					
	30-40 (*n*=3)	41-50 (*n*=34)	51-60 (*n*=114)	61-70 (*n*=150)	71-80 (*n*=91)	81-90 (*n*=6)
No. of patients with nausea (%)	3 (100)	14 (41)	38 (33)	50 (33)	32 (35)	1 (17)
No. of patients with retching or vomiting (%)	2 (67)	12 (35)	29 (25)	41 (27)	26 (29)	0 (0)

There were highly significant differences in the incidence of PONV between the two groups. Addition of droperidol to infusion of morphine was associated with a reduction in complaints of nausea from 92 of 198 (46.5%) to 46 of 200 (23%) and in episodes of retching or vomiting from 73 of 198 (36.9%) to 44 of 200 (22%). The number of patients requiring rescue medication was also significantly reduced from 100 of 198 (50.5%) of those not receiving droperidol to 44 of 200 (22%) of those given droperidol (table 3). There was no correlation between body mass index and propensity for nausea or vomiting.

When data were examined to investigate the influence of sex on nausea and vomiting, it became apparent that women were significantly more likely than men to suffer nausea, retching and vomiting (table 4). Although droperidol was effective in significantly decreasing retching and vomiting in women, it did not significantly reduce the incidence of nausea. This last observation may be related to the relatively small number of women in the sample, reducing the power of the measurement.

Data were also examined to assess the effect of age on PONV (table 5). There was a statistically significant reduction in the incidence of PONV in patients more than 80 yr of age.

Discussion

It is important to minimize vomiting and retching after surgery to avoid potential cardiovascular complications and to improve patient comfort and assist in rapid recovery. The latter is of particular importance with increasing financial pressure and the drive to reduce inpatient stay[2]. While there was no significant difference in the length of stay in the CRU between vomiters and non-vomiters, this is not surprising as PONV is unlikely to be a problem requiring an increase in the length of high dependency nursing.

Until about 6 yr ago it was our standard practice to sedate patients after cardiac surgery and to ventilate the lungs for a period of 12–16 h after operation. Nausea and vomiting were not perceived as particular problems with this regimen, and it is possible that a lengthy period of sedation and artificial ventilation reduced the incidence of postoperative emesis. More recently, we have tended to extubate the trachea much earlier after surgery[3] and have become increasingly aware of the problem of PONV. Our study has shown that using a moderate dose of fentanyl, and extubating the trachea within the first 6–8 h after cardiac surgery, the incidence of nausea was approximately 37% and that of postoperative retching or vomiting approximately 47%, despite the use of hyoscine as premedication. The overall incidence of nausea and vomiting was therefore of a similar order to that after other types of major surgery[4].

In common with Myles and colleagues[5], we have found that many of our patients are unable to use patient-controlled analgesia effectively in the first 24 h after cardiac surgery, and we therefore rely on a nurse-controlled regimen for the early postoperative period. Addition of droperidol to infusion of morphine reduced significantly the incidence of nausea and approximately halved the incidence of retching and vomiting. While it has been argued that prophylactic administration of antiemetics is unjustified[6], in view of the high incidence of PONV and its potential deleterious effects after cardiac surgery, the prophylactic use of droperidol has now become part of our standard practice.

Droperidol is a neuroleptic agent with potent dopamine receptor antagonist properties and is an effective antiemetic in a variety of doses. Bolus doses are contraindicated after cardiac surgery as its α blocking actions may cause hypotension. Low doses of droperidol have been shown to effectively reduce the incidence of postoperative nausea and vomiting when mixed with morphine and used for patient-controlled analgesia[7–9] and it has been suggested as the agent of choice for prophylaxis[10]. Newer 5-HT_3 antagonist drugs have not been shown to be significantly more effective[11] and are considerably more expensive.

Droperidol has a long duration of action and is associated with sedation and extrapyramidal reactions. When used in combination with morphine for patient-controlled analgesia, addition of droperidol appears to cause significantly greater sedation[12 13], although in single low doses it has been shown to have no effect on recovery time[14]. We were concerned that routine use of droperidol might prolong the duration of intubation after cardiac surgery. Although we did not measure sedation scores, we found that the use of droperidol had no effect on duration of postoperative intubation, nor did it prolong patient stay in the CRU. The mean dose of droperidol was approximately 5 mg during a mean stay of 21.9 h, that is approximately 0.23 mg h^{-1}. While we would not dispute that there may have been some increase in sedation which was not measured, the sedative effects were not clinically important.

In common with most other studies of vomiting, we found that both nausea and vomiting were associated significantly with female sex. Lerman[15] has suggested that the incidence of PONV is approximately 2–3 times greater in women than in men. In this study, PONV appeared to be about 1.5–2 times more common in women.

When the effect of age on the incidence of nausea and vomiting was examined, although the number of patients aged more than 80 yr was small, octogenarians suffered significantly less PONV than younger patients. At the lower end of the age range there were only three patients aged less than 40 yr but all three suffered nausea and two vomited. Thus it appears that age does have some effect on the propensity for PONV after heart surgery.

While obesity has been reported to increase PONV[4], in contrast with other studies[17], we did not show any correlation between body mass index and nausea and vomiting.

In summary, we found that the incidence of PONV after cardiac surgery was similar to that after other major surgical procedures. We also observed that the addition of droperidol to a continuous infusion of morphine significantly reduced the incidence of nausea and vomiting after cardiac surgery without prolonging the duration of intubation or postoperative intensive care stay.

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References

1. Chong JL, Pillai R, Fisher A, Grebenik C, Sinclair M, Westaby S. Cardiac surgery: moving away from intensive care. *British Heart Journal* 1992; **68**: 430–433.
2. Krohn BG, Kay JH, Mendez MM, Zubiate P, Kay GL. Rapid sustained recovery after cardiac operations. *Journal of Thoracic and Cardiovascular Surgery* 1990; **100**: 194–197.

3. Chong JL, Grebenik C, Sinclair M, Fisher A, Pillai R, Westaby S. The effect of a cardiac surgical recovery area on the timing of extubation. *Journal of Cardiothoracic and Vascular Anesthesia* 1993; 7: 1–5.
4. Palazzo MGA, Strunin L. Anaesthesia and emesis. I: Aetiology. *Canadian Anaesthetists Society Journal* 1984; **31**: 178–187.
5. Myles PS, Buckland MR, Cannon GB, Bujor MA, Langley M, Breaden A, Salamonsen RF, Davis BB. Comparison of patient-controlled analgesia and nurse controlled infusion analgesia after cardiac surgery. *Anaesthesia and Intensive Care* 1994; **22**: 672–678.
6. Adriana J, Summers FW, Anthony SO. Is the prophylactic use of antiemetics in surgical patients justified? *Journal of the American Medical Association* 1961; 175: 666–671.
7. Barrow PM, Hughes DG, Redfern N, Urie J. Influence of droperidol on nausea and vomiting during patient-controlled analgesia. *British Journal of Anaesthesia* 1994; 72: 460–461.
8. Sharma SK, Davies MW. Patient-controlled analgesia with a mixture of morphine and droperidol. *British Journal of Anaesthesia* 1993; 71: 435–436.
9. Roberts CJ, Millar KM, Goat VA. The antiemetic effectiveness of droperidol during morphine patient-controlled analgesia. *Anaesthesia* 1995; **50**: 559–562.
10. Palazzo MGA, Strunin L. Anaesthesia and emesis. II: Prevention and management. *Canadian Anaesthetists Society Journal* 1984; **31**: 407–415.
11. Gan TJ, Collis R, Hetreed M. Double-blind comparison of ondansetron, droperidol and saline in the prevention of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1994; 72: 544–547.
12. Williams OA, Clarke FL, Harris RW, Smith P, Peacock JE. Addition of droperidol to patient controlled analgesia: effect on nausea and vomiting. *British Journal of Anaesthesia* 1993; **48**: 881–884.
13. Gan TJ, Alexander R, Fennelly, M, Rubin AP. Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of postoperative nausea and vomiting. *Anesthesia and Analgesia* 1995; **80**: 81–85.
14. Jorgensen NH, Coyle JP. Intravenous droperidol decreases nausea and vomiting after alfentanil anesthesia without increasing recovery time. *Journal of Clinical Anesthesia* 1990; **2**: 312–316.
15. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 24S–32S.
16. McKenzie R, Wadhwa RK, Ly NTL, Phitayakorn P, Tantisira B, Sinchioco C, Taylor FH. Antiemetic effectiveness of intramuscular hydroxyzine compared with intramuscular droperidol. *Anesthesia and Analgesia* 1981; **60**: 783–788.

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Cardiopulmonary bypass-induced changes in plasma concentrations of propofol and in auditory evoked potentials†

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Summary

Unbound, rather than total, plasma concentrations may be related to the anaesthetic action of propofol. Therefore, we measured plasma concentrations of propofol and recorded Nb wave latencies of auditory evoked potentials (AEP) during continuous infusion of propofol in 15 patients undergoing coronary artery bypass grafting (CABG) surgery. After induction of anaesthesia with fentanyl, propofol was infused continuously at a rate of 10 mg kg^{-1} h^{-1} for 20 min, and then the rate was reduced to 3 mg kg^{-1} h^{-1}. Administration of heparin before cardiopulmonary bypass (CPB) did not affect total or unbound propofol concentration. Initiation of CPB decreased mean total propofol concentration from 2.6 to 1.7 μg ml^{-1} ($P<0.01$). Simultaneously, mean unbound propofol concentration remained at 0.06 μg ml^{-1} because of a slight increase in the mean free fraction of plasma propofol (from 2.3 to 3.5%; $P>0.05$). During hypothermic CPB, mean total propofol concentration increased to concentrations measured before bypass (to 2.1 μg ml^{-1}; $P>0.05$ *vs* value before CPB) and the mean unbound propofol concentration was at its highest (0.07 μg ml^{-1}; $P<0.05$ *vs* value before heparin). After CPB and administration of protamine, the mean total propofol concentration remained lowered (1.7 μg ml^{-1}; $P<0.05$ *vs* value before heparin) and the mean unbound propofol concentration returned to the level measured before heparin ($P<0.001$ *vs* value during hypothermia). The latency of the Nb wave from recordings of AEP increased after induction of anaesthesia, reached its maximum during hypothermia and was prolonged during the subsequent phases of the study. The latency of the Nb wave did not correlate with total or unbound propofol concentration. We conclude that the changes in total and unbound concentrations of plasma propofol were not parallel in patients undergoing CABG. During CPB or at any other time during the CABG procedure, the unbound propofol concentration did not decrease and Nb wave latency was prolonged compared with baseline values measured after induction of anaesthesia before the start of CPB. (*Br. J. Anaesth.* 1996;**77**:360–364)

Key words

Anaesthetics i.v., propofol. Heart, cardiopulmonary bypass. Brain, evoked potentials. Pharmacodynamics. Surgery, cardiovascular.

Mean total propofol concentrations of greater than 1 μg ml^{-1} in whole blood[1] and plasma[2] in conjunction with administration of opioids, have been reported to be associated with sufficient depth of anaesthesia to prevent recall of awareness in cardiac surgical patients. The measured total drug concentration may not represent adequate drug action in all circumstances and it may be important to consider also the unbound drug concentration, especially with drugs that are bound to plasma proteins to a high degree[3], such as propofol, with a bound fraction of 97–98% in healthy subjects[4]. It would be important to determine unbound plasma drug concentration in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), because in these patients there are several factors that may affect plasma concentrations and protein binding of drugs[2 5–7]. In this study, therefore, unbound and total plasma concentrations of propofol were measured during cardiac surgery in patients receiving a continuous infusion of propofol as a supplement to fentanyl-based anaesthesia. We recorded also auditory evoked potentials (AEP) and measured the latency of the Nb wave[8] as a possible indicator of anaesthetic depth, at the same times as propofol concentrations.

Patients and methods

The study was approved by the local Ethics Committee and informed consent was obtained from each patient. We studied 19 patients undergoing elective coronary artery bypass grafting (CABG) surgery. All patients had a preoperative left ventricular ejection fraction >40%. After initial inclusion, one patient was excluded because of hypotension and difficulty in weaning from extracorporeal circulation and three patients because of technical problems in the measurement of auditory evoked potentials. Thus 15 patients completed the study, but three were excluded from the AEP analyses because of electrically contaminated measurements or difficulties in identifying the Nb wave adequately at some times. The characteristics of the 15 patients are given in table 1. On the morning of operation, patients received their regular doses of β adrenergic blockers,

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calcium channel blockers and long-acting nitrates. Two hours before arrival in the operating theatre, patients were premedicated with lorazepam 60 μg kg^{-1} orally, approximated downwards to the nearest milligram.

Anaesthesia was induced with fentanyl 30 μg kg^{-1} and diazepam 0.1 mg kg^{-1} and thereafter an infusion of fentanyl was started at a rate of 0.2 μg kg^{-1} min^{-1}. Neuromuscular block was produced with pancuronium 0.1 mg kg^{-1}. After induction of anaesthesia, the trachea was intubated and the lungs ventilated mechanically with a mixture of oxygen and air ($F_{I_{O_2}}$ 0.50). After induction of anaesthesia, a continuous infusion of propofol 10 mg kg^{-1} h^{-1} was given for 20 min and thereafter the infusion rate was reduced to 3 mg kg^{-1} h^{-1} which was continued until the end of the study (5 min after administration of protamine). The infusion rates of propofol were chosen according to previous studies in patients undergoing cardiac surgery with opioid-based anaesthesia[1 2]. Ephedrine and nitroglycerin were given before and after CPB in increments of 5 mg and 100–200 μg, respectively, to maintain systolic arterial pressure at 80–150 mm Hg. The degree of neuromuscular block was estimated visually according to the train-of-four principle, using 2 Hz supramaximal stimulation of the ulnar nerve. Incremental doses of pancuronium (1–2 mg) were given to maintain block within 90–95%. Normocapnia was maintained by monitoring end-tidal carbon dioxide concentration continuously and by measuring arterial P_{CO_2} intermittently. During CPB, the lungs were ventilated to ambient air.

For CPB, we used non-pulsatile pump flow, membrane oxygenation, moderate hypothermia (nasopharyngeal temperature 30 °C) and isovolaemic haemodilution. Myocardial protection during aortic cross-clamping was achieved with cold, crystalloid potassium cardioplegia solution (Plegisol, Abbott, North Chigago, IL, USA) given anterogradely and intermittently. Systemic anticoagulation was produced with an initial dose of heparin 300 u. kg^{-1} and with subsequent additional doses of heparin to maintain blood activated clotting time (ACT) >480 s. During the cooling and rewarming phases of CPB, pump flow was 2.4 litre min^{-1} m^{-2} and during the hypothermic phase 1.8 litre min^{-1} m^{-2}. After CPB, heparin anticoagulation was neutralized with protamine sulphate 3 mg kg^{-1}.

Blood samples for measurement of plasma propofol and serum albumin concentrations and blood packed cell volume (PCV) were obtained from the radial artery into prechilled heparinized tubes at the following times: (1) after induction of anaesthesia before administration of heparin, when propofol had been infused for a mean time of 57 (95% confidence interval 48–66) min; (2) 5 min after administration of the initial dose of heparin before the start of CPB; (3) 1 min after the start of CPB; (4) during hypothermic CPB when nasopharyngeal temperature had stabilized to 30 °C; (5) after CPB before administration of protamine; and (6) 5 min after administration of protamine. The samples were centrifuged within 20 min at +4 °C at 3000 rpm for 10 min and plasma was stored at −70 °C until assayed. The unbound fraction of plasma propofol was separated by equilibrium dialysis at 37 °C, as described by Teh and colleagues[9]. The dialysis membrane was Spectra/Por, with a molecular weight cut-off of 12 000–14 000 (Spectrum Medical Industries, Inc. Houston, TX, USA). After dialysis, both plasma and buffer fractions were analysed separately for propofol concentration[4]. The detection limit was approximately 3 ng ml^{-1}. The within-day coefficient of variation of the assay of relevant concentrations was 6% or less. The unbound fraction of propofol was calculated as the ratio of unbound to total propofol concentration.

Table 1 Characteristics of the 15 patients (mean (range or 95% confidence interval) or number of patient)

Age (yr)	60 (range 43–70)
Weight (kg)	83 (75–91)
Height (cm)	171 (167–176)
Ejection fraction of left ventricle (%)	55 (49–61)
Sex (M/F)	13/2
Preoperative medication	
Long-acting nitrates	13
Calcium channel blockers	6
β adrenergic blockers	14
Aortic cross-clamp time (min)	64 (54–76)
Cardiopulmonary bypass time (min)	95 (81–110)

AUDITORY EVOKED POTENTIALS

We used the Neuropack Four Mini (Nihon Kohden, Japan) evoked potential device for acoustic stimulation and recording of evoked potentials. Rarefaction clicks of 0.1 ms and 90 dB above the normal hearing level were presented monaurally to the patient's ear via headphones at a rate of 7.0 Hz. For recording, silver–silver chloride cup electrodes were positioned at the Fz point (frontal lead) and contralateral ear lobe with an extracephalic ground. Inter-electrode impedances were maintained less than 5.0 kΩ and the amplification bandpass was set at 20–1000 Hz. Evoked potential latencies of Nb waves were measured offline, after randomization, by one of the authors (A.Y.-H.) blinded to the measurement times. The auditory responses (two averages of 500 epochs) were recorded before induction of anaesthesia and also at the same six times as the samples for measurement of propofol concentrations (see above). To exclude any impairment in hearing function, conventional air conduction audiometry at frequencies of 0.25–8 kHz was performed on the day before operation.

OTHER MEASUREMENTS

Heart rate, mean arterial pressure (MAP) and other clinical signs of depth of anaesthesia (movement, sweating, tearing), and nasopharyngeal and rectal temperatures were measured at the same times as the AEP recordings. All patients were interviewed after operation for evaluation of intraoperative awareness and recall of intraoperative events.

STATISTICAL ANALYSIS

Analysis of variance for repeated measures was used to detect significant changes in the variables over time. Analysis of covariance for repeated measures was used to define the relationship between total or unbound propofol concentrations in plasma and auditory evoked latencies and the relationship between the ratio of bound to unbound propofol concentration in plasma to blood PCV or serum albumin concentration. For subsequent multiple comparisons, Tukey's method was used[10]. $P<0.05$ was considered statistically significant. Results are expressed as mean (95% confidence intervals or range).

Results

EFFECT OF HEPARIN

Administration of heparin did not change the total plasma concentration of propofol (table 2). Simultaneously, because the mean unbound fraction of propofol increased by 53%, the mean unbound propofol concentration increased by 64%. However, these increases were not significant.

EFFECT OF CPB

Initiation of CPB decreased the total concentration of propofol ($P<0.01$ *vs* value after heparin) (table 2). Concomitantly, because the unbound fraction of propofol tended to increase, the unbound propofol concentration did not change. Compared with the value before heparin, the unbound fraction of propofol was significantly ($P<0.01$) increased 1 min after the start of CPB. During hypothermic CPB, the mean values of unbound propofol concentration and the unbound fraction of propofol were at their highest ($P<0.05$ and $P<0.01$, respectively, compared with values before heparin).

POST-CPB PHASE

After CPB, both before and after administration of protamine, total propofol concentration was lower than values before CPB ($P<0.05$ *vs* value before heparin and $P<0.01$ *vs* value after heparin) (table 2). Administration of protamine had no significant effect on either total or unbound propofol concentration. However, after administration of protamine the unbound propofol concentration was at its lowest ($P<0.001$ compared with value during hypothermic CPB). After administration of protamine, the unbound fraction had returned to baseline values, that is to the level observed before administration of heparin, and the unbound fraction was significantly ($P<0.01$) lower compared with the value during hypothermic CPB.

BLOOD PACKED CELL VOLUME AND SERUM ALBUMIN

Blood PCV and serum albumin concentration were unchanged during the period before bypass. After commencement of CPB, the values of these variables decreased significantly ($P<0.001$) and remained decreased during CPB. After CPB and administration of protamine, PCV and serum albumin concentration increased ($P<0.01$ and $P<0.05$, respectively) from values measured during hypothermic CPB, but they remained lower ($P<0.001$) than those observed before CPB (table 2). The ratio of bound to unbound propofol concentration was not related significantly to serum albumin concentration ($P=0.62$) or PCV ($P=0.23$).

NB WAVE OF THE AUDITORY EVOKED POTENTIALS

Induction of anaesthesia increased the latency of the Nb wave ($P<0.001$) and thereafter it remained prolonged until the end of the study (table 2). During the hypothermic phase of CPB, the latency of the Nb wave was increased compared with the value before the start of CPB ($P<0.05$). After CPB, the latency of the Nb wave shortened to the level measured before the start of CPB. The latency of the Nb wave was not significantly related to the total or unbound propofol concentration.

Table 2 Plasma total and unbound propofol concentration, unbound fraction of propofol-packed cell volume (PCV), serum albumin concentration and latency of the Nb wave from the AEP (mean (95% confidence interval)). $n=15$ patents, unless otherwise indicated ($^1n=14$, $^2n=12$)). NA = not available. $^*P < 0.05$ *vs* value awake; † $P < 0.05$ *vs* value before heparin; ‡$P < 0.05$ *vs* value before CPB; §$P < 0.05$ *vs* hypothermic CPB

	Awake	Before heparin	After heparin, before CPB	During CPB (1 min)	During hypothermic CPB	After CPB, before protamine	After protamine
Time from awake sample (min)		87 (79–95)	96 (87–105)	113 (104–121)	142 (131–153)	210 (194–225)	228 (211–244)
Total propofol (μg ml^{-1})	NA	2.4 (2.1–2.7)	2.6 (2.3–2.8)	1.7 (1.5–2.0)†‡	2.1 (1.7–2.4)	1.7 (1.4–2.0)†‡	1.7 (1.5–2.0)†‡
Unbound propofol (μg ml^{-1})	NA	0.04 (0.03–0.04)	0.06 (0.040.07)	0.06 (0.040.07)	0.07 (0.040.10)†	0.04 (0.030.05)	0.02 (0.020.03)‡§
Plasma unbound fraction (%)	NA	1.5 (1.1–1.9)	2.3 (1.7–2.9)	3.5 (2.5–4.5)†	3.7 (2.3–5.1)†	2.6 (1.9–3.3)	1.5 (1.2–1.7)§
Blood PCV	NA	0.37 (0.35–0.39)	0.37 (0.34–0.39)	0.25 (0.23–0.27)†‡	0.25 (0.24–0.27)†‡	0.28 (0.26–0.30)†‡	0.29 (0.28–0.30)†‡§
Serum albumin (g litre^{-1})^1	NA	36 (34–38)	37 (35–39)	22 (19–24)†‡	21 (18–23)†‡	24 (22–26)†‡§	25 (24–27)†‡§
Latency of Nb wave (ms)^2	41 (33–48)	71 (67–74)*	67 (62–71)*	73 (68–77)*	79 (73–85)*‡	66 (65–68)*§	70 (65–76)*

Table 3 Heart rate, mean arterial pressure (MAP), sweating, tearing, and nasopharyngeal (*T*naso) and rectal (*T*rect) temperatures (mean or number of patients (95% confidence interval). n=15 patients, unless otherwise indicated ([i]n=9, six patients were excluded because of the need for artificial pacing after CPB)). NA=not available

	Awake	Before heparin	After heparin, before CPB	During CPB (1 min)	During hypothermic CPB	After CPB, before protamine	After protamine
Heart rate (beat min^{-1})	61 (56–66)	62 (56–67)	65 (59–71)	NA	NA	95 (89–101)	94 (84–104)
MAP (mm Hg)	91 (88–94)	79 (71–86)	79 (68–90)	67 (56–78)	63 (52–73)	61 (58–64)	72 (66–78)
Sweating	0	2	2	0	0	0	0
Tearing	0	0	0	0	0	0	0
*T*naso (°C)	NA	35.2 (35.0–35.5)	35.2 (35.0–35.4)	34.0 (33.9–34.3)	30.1 (30.0–30.2)	37.5 (37.2–37.8)	36.4 (36.1–36.8)
*T*rect (°C)	NA	35.8 (35.6–36.0)	35.8 (35.6–36.0)	35.1 (34.8–35.4)	32.4 (31.9–32.9)	36.4 (36.1–36.7)	36.5 (36.2–36.8)

OTHER CLINICAL SIGNS

Data for other clinical signs are given in table 3. Before the start of CPB during surgery, two patients were sweating slightly (skin on the forehead moist, no visible beads of perspiration). Movement or tearing was not detected in any patient. Two patients needed increments of nitroglycerin because of hypertension before CPB. There was no recall of conscious awareness of intraoperative events reported by any patient.

Discussion

We have observed that the changes in plasma total and unbound propofol concentrations were not parallel during cardiac surgery. The most prominent differences in the changes were observed during CPB.

The decrease in total propofol concentration with initiation of CPB was probably mainly a result of the haemodiluting effect of the priming solution in the extracorporeal circuit. Binding of propofol to the extracorporeal circuit may be an additional factor in decreasing plasma concentration of propofol in patients undergoing CPB[2]. Decrease in total drug concentration with initiation of CPB has been demonstrated previously with various drugs[5,6,11], including propofol[1,2]. In spite of the decrease in total propofol concentration, we did not notice any decrease in the unbound propofol concentration when CPB was started because the free fraction of plasma propofol increased. Russell and co-workers[1] also observed a significant increase in the free fraction of plasma propofol concentration caused by CPB, but they did not report the unbound concentrations. During the later phase of CPB at 30 °C, total propofol concentration increased to pre-bypass values from values measured immediately after commencement of CPB and unbound propofol concentration was at its highest. These increases in propofol concentration may have resulted from decreases in volume of distribution and clearance of propofol during hypothermia[7]. Russell and co-workers[1] also described an "upward trend" in total propofol concentration during hypothermic CPB.

Administration of heparin tended to increase the free fraction of propofol in plasma and a reversed change was observed after protamine. Although the changes observed in this study were not significant, heparin and subsequent neutralization with protamine have been reported to affect significantly the unbound fraction of various other drugs in cardiac surgery patients[6,11,12]. Heparin activates lipoprotein lipase to hydrolyse plasma triglycerides into non-esterified fatty acids[13]. These compounds competitively inhibit the binding of various drugs to plasma proteins and may be attributed to the increase in the unbound fraction of the drug.

It has been suggested that the depth of anaesthesia can be measured with AEP during anaesthesia with various anaesthetic agents[8,14–16]. We chose to measure, among all the AEP variables, the latency of the Nb wave, which may be one of the most reliable variables to indicate the adequacy of anaesthesia, that is loss of consciousness[14,15]. In this study, the means of the latencies of the Nb wave at different recording times during anaesthesia were significantly prolonged compared with the latency while awake, suggesting an adequate level of anaesthesia. Accordingly, there was no recall of conscious awareness of intraoperative events reported by any patient. The deepest level of anaesthesia probably occurred during hypothermic CPB; at this stage Nb latency was longest and the unbound propofol concentration greatest. However, we found no correlation between the latency of Nb wave and total or unbound propofol concentration. This was probably because of simultaneous infusion of fentanyl and to some extent other confounding factors during cardiac surgery, such as hypothermia during CPB[17], altered cerebral blood flow during CPB and changes in surgical stimulation.

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References

1. Russell GN, Wright EL, Fox MA, Douglas EJ, Cockshott ID. Propofol–fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. *Anaesthesia* 1989; **44**: 205–208.
2. Hynynen M, Hammarén E, Rosenberg PH. Propofol sequestration within the extracorporeal circuit. *Canadian Journal of Anaesthesia* 1994; **41**: 583–588.
3. Rolan PE. Plasma protein binding displacement interactions—why are they still regarded as clinically important? *British Journal of Clinical Pharmacology* 1994; **37**: 125–128.
4. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology* 1988; **69**: 887–891.

5. Morgan DJ, Crankshaw DP, Prideaux PR, Chan HNJ, Boyd MD. Thiopentone levels during cardiopulmonary bypass. Changes in plasma protein binding during continuous infusion. *Anaesthesia* 1986; 41: 4–10.
6. Hynynen M, Hynninen M, Soini H, Neuvonen PJ, Heinonen J. Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *British Journal of Anaesthesia* 1994; 72: 571–576.
7. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *British Journal of Anaesthesia* 1995; 75: 344–351.
8. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; 8: 89–107.
9. Teh J, Short TG, Wong J, Tan P. Pharmacokinetic interactions between midazolam and propofol: an infusion study. *British Journal of Anaesthesia* 1994; 72: 62–65.
10. Tukey JW. Comparing individual means in the analysis of variance. *Biometrics* 1949; 5: 99–114.
11. Hynynen M, Siltanen T, Sahlman A, Pohjasvaara T, Mück W, Kaste M. Continuous infusion of nimodipine during coronary artery surgery: haemodynamic and pharmacokinetic study. *British Journal of Anaesthesia* 1995; 74: 526–533.
12. Wood M, Shand DG, Wood AJJ. Propranolol binding in plasma during cardiopulmonary bypass. *Anesthesiology* 1979; 51: 512–516.
13. Giacomini KM, Swezey SE, Giacomini JC, Blaschke TF. Administration of heparin causes in vitro release of nonesterified fatty acids in human plasma. *Life Sciences* 1980; 27: 771–780.
14. Thornton C, Barrowcliffe MP, Konieczko KM, Vetham P, Doré CJ, Newton DEF, Jones JG. The auditory evoked response as an indicator of awareness. *British Journal of Anaesthesia* 1989; 63: 113–115.
15. Newton DEF, Thornton C, Konieczko KM, Jordan C, Webster NR, Luff NP, Frith CD, Doré J. Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane. *British Journal of Anaesthesia* 1992; 69: 122–129.
16. Schwender D, Rimkus T, Haessler R, Klasing S, Pöppel E, Peter K. Effects of increasing doses of alfentanil, fentanyl, and morphine on mid-latency auditory evoked potentials. *British Journal of Anaesthesia* 1993; 71: 622–628.
17. Hett DA, Smith DC, Pilkington SN, Abbott TR. Effect of temperature and cardiopulmonary bypass on the auditory evoked response. *British Journal of Anaesthesia* 1995; 75: 293–296.

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On-line estimation of left ventricular stroke volume using transoesophageal echocardiography and acoustic quantification

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Summary

We have examined the usefulness of transoesophageal echocardiography (TOE) and automated endocardium detection for on-line calculation of left ventricular stroke volume. In 12 of 15 patients undergoing abdominal surgery, stroke volume was derived continuously from the multiple discs (MD) and area–length (AL) methods and compared with stroke volume calculated by thermodilution. In 10 patients (80%), more than three manipulations of the ultrasound transducer were required before measurements. Linear regression analysis of automated TOE methods and thermodilution revealed weak correlations (r<0.75) for stroke volume (114 matched pairs) and its changes (105 matched pairs). Correlation of percentage changes in stroke volume calculated by thermodilution with those derived from MD (r=0.85) and AL (r=0.79) was better. Changes in MD (AL) derived stroke volume by more than 20% identified changes in thermodilution-derived stroke volume greater than 20% (n=57) with a sensitivity of 74% (70%) and a specificity of 82% (79%). Signal instability, lack of accuracy and only a moderate trend capability currently limit the intraoperative usefulness of automated TOE techniques for continuous estimation of stroke volume from a single long-axis plane. (*Br. J. Anaesth.* 1996;**77**:365–369)

Key words

Heart, myocardial function. Heart, ventricles. Measurement techniques, acoustic quantification. Monitoring, echocardiography.

Echocardiographic automated border detection (ABD), which is based on the acoustic quantification of ultrasonic back scatter signals[1], has recently been added to the intraoperative assessment of left ventricular (LV) function[2-4]. ABD algorithms have been devised to derive real-time LV volumes from single-plane long-axis views on a beat-to-beat basis. This technique uses previously established area–length (AL) or multiple disc (MD) formulae[5-6] and provides the user with digitized information on end-diastolic and end-systolic LV volume. Few transthoracic studies have investigated the potential of ABD methods for rapid on-line calculation of LV stroke volume[7-9]. This study was designed to assess the capability of ABD techniques for transoesophageal (TOE) monitoring of LV stroke volume during prolonged surgical procedures.

Patients and methods

After obtaining approval from the local Ethics Committee, we studied 15 consenting patients (aged 37–62 yr) undergoing prolonged major abdominal surgery. Measurement of cardiac output by thermodilution using a pulmonary artery catheter (7.5 F, Baxter Healthcare Corp., Irvine, CA, USA) was part of the routine anaesthetic management. All observations were made with the heart in sinus rhythm.

After induction of anaesthesia and tracheal intubation, a 5-MHz multiplane ultrasound transducer connected to an imaging system with an endocardial edge detection algorithm (Sonos 1500, Hewlett Packard, Andover, MA, USA) was introduced into the oesophagus. After a routine echocardiographic examination, the probe was positioned at the midoesophageal level and the transducer crystals rotated electronically (40–80°) until the two-chamber view with the longest LV axis was seen without imaging the LV outflow tract. This image was stored as cine loop for later reference. ABD was activated, and transmission, time-gain compensation and lateral gain control adjusted to obtain optimal back scatter imaging of the endocardium. Gain settings were maintained unchanged throughout the study. After limiting the region of interest, LV volumes at end-diastole and end-systole were calculated continuously and displayed (fig. 1) by a prototype software package integrated into the ultrasound system. The transducer was fixed at the operating table and its position corrected before each measurement of cardiac output when required to regain the reference two-chamber view. Studies were eliminated from analysis when ABD failed to detect more than 75% of the endocardial edge, compared visually with the standard two-dimensional image, or when regional wall motion abnormalities were detected. Real-time volumes were estimated from this view by two algorithms activated independently

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(fig. 1). The method of discs (MD), a modification of Simpson's rule, allowed automated volume calculation from 20 equally spaced discs. The second was the area–length (AL) formula. MD and AL derived stroke volumes were calculated off-line as the difference between end-diastolic and end-systolic LV volume.

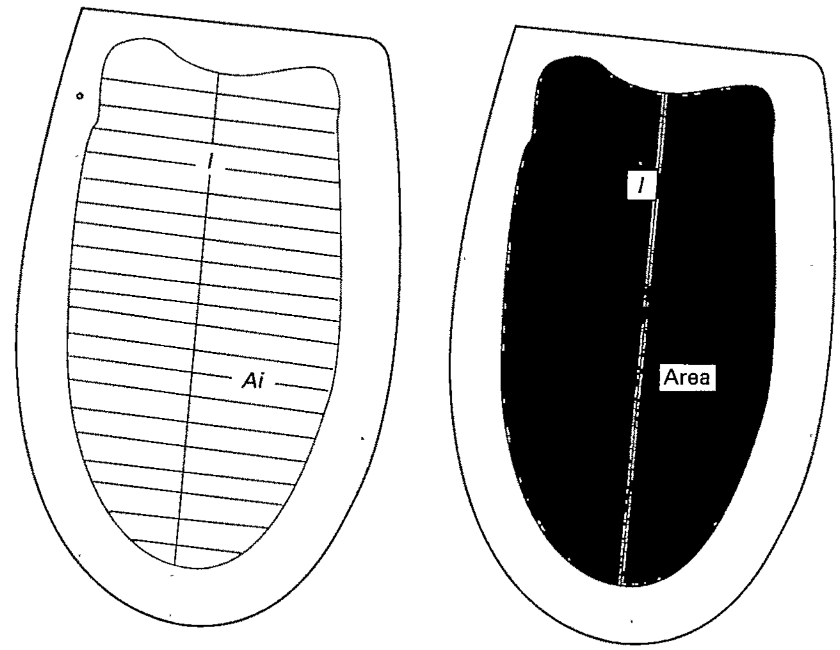
Measurements of cardiac output by thermodilution were performed in triplicate during expiration using 10 ml of iced saline. Values of 15% variation, largest to smallest, were accepted for calculating mean cardiac output and mean stroke volume as the ratio of cardiac output and heart rate. Corresponding to each thermodilution bolus, echocardiographic sequences of at least 10 cardiac cycles were recorded on videotape. During a minimum operation time of 4 h, a total of 10–14 mean cardiac output measures and serial echocardiograms were obtained for each patient. Measurements were made at intervals of approximately 15 min or at the request of the attending anaesthetist.

Videotape recordings were analysed by taking 25 consecutive cardiac cycles from each series of echocardiograms corresponding to each measurement of mean cardiac output by thermodilution. Mean values of MD and AL derived stroke volume were compared with stroke volume calculated by thermodilution by linear regression, Bland–Altman analysis[10] and analysis of variance (ANOVA). Changes in MD and AL derived stroke volume were tested for sensitivity and specificity of indicating clinically relevant changes in thermodilution stroke volume (defined as changes of more than 20%). To account for the variability in ABD determined LV volumes, we calculated 95% confidence limits of LV stroke volume, obtained from 25 consecutive cardiac cycles at each measurement. Only stroke volume data with a confidence range of less than ±20% from the mean were accepted for direct comparison with thermodilution stroke volume. Consequently, only changes in mean ABD derived stroke volume of more than 20% were considered significant.

Results

Technically adequate echocardiograms with activated ABD were obtained in 12 patients within a few minutes after insertion of the probe. Three additional patients were excluded after being entered into the study because intraoperative echocardiographic criteria were not fulfilled. In 10 patients (83%) more than three measurements required prior manipulations of the probe to correct for the pre-selected view or regain good image quality. In total, 114 corresponding measurements of ABD and thermodilution derived stroke volume (range 37–161 ml) and 105 calculations of stroke volume changes (−65–117 ml) were available for comparison; 16% of all ABD data were excluded from comparison because of unacceptable variability.

Underestimation of thermodilution stroke volume by ABD methods occurred throughout the study in all but one patient. Linear regression analysis revealed poor correlation between both ABD methods and thermodilution in determining stroke volume (r=0.66 and r=0.68). Results of Bland–Altman analysis showed a mean systematic stroke volume difference of approximately 25 ml (fig. 2), with mean estimation of cardiac output being 2.5 litre min^{-1} less than cardiac output calculated by thermodilution. No significant effects of heart rate, end-systolic or end-diastolic volume were detected between the methods. Changes in thermodilution stroke volume correlated moderately with those for



Method of discs
$V = n\pi l/4l \sum_{l=1}^{n} Ai^2$

Area–length method
$V = 8\ \text{area}^2/3\pi l$

Figure 1 Transoesophageal echocardiographic view of the left ventricle in its long axis. Left: Single-plane application of the method of discs allowed calculation of the volume of the left ventricle from 20 equally spaced discs (*Ai*, with *i*=1 to *i*=20) and the length of the long chamber axis (*l*). Right: Single-plane application of the area–length method allowed calculation of the volume of the left ventricle from the cross-sectional chamber area and long axis chamber length (*l*).

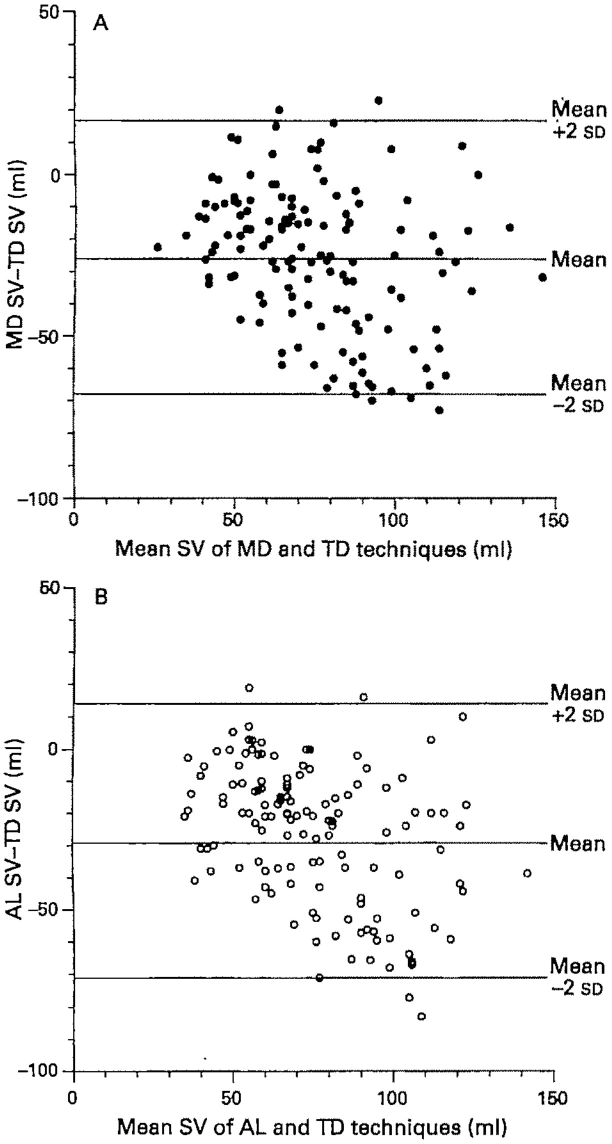


Figure 2 Bias analysis of stroke volume (SV) obtained by thermodilution (TD), and (A) the multiple disc (MD) method (mean –26 (SD 21) ml) and (B) the area–length (AL) method (–28 (22) ml).

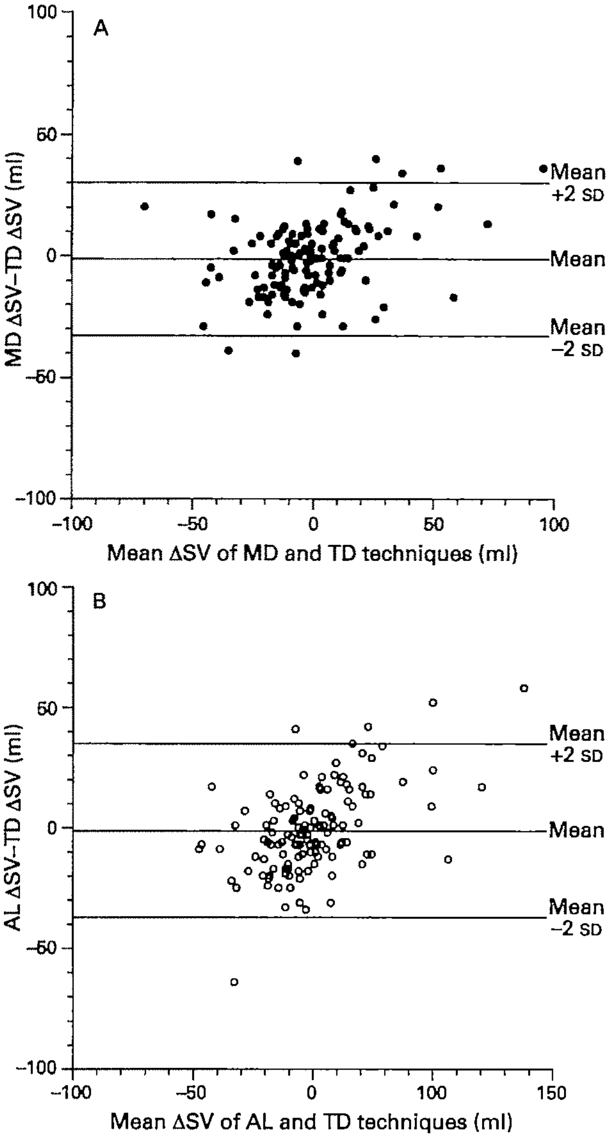


Figure 3 Bias analysis of changes in stroke volume (ΔSV) obtained by thermodilution (TD), and (A) the multiple disc (MD) method (mean –1 (SD 18) ml) and (B) the area–length (AL) method (–1 (16) ml).

MD and AL derived stroke volume (r=0.75 and r=0.69). However, Bland–Altman analysis revealed high standard deviations for both ABD methods (fig. 3). Significant good correlations between ABD methods and thermodilution were obtained for percentage changes in stroke volume (fig. 4).

Direction of changes in thermodilution stroke volume were indicated correctly in 79% (MD method) and 72% (AL method) of all measurements. Changes in MD derived stroke volume (AL stroke volume) by more than 20% identified thermodilution stroke volume changes greater than 20% (n=57) with a sensitivity of 74% (70%) and a specificity of 82% (79%). The mean positive predictive value of significant ABD derived stroke volume changes for thermodilution stroke volume changes >20% was 0.60. The mean negative predictive value of non-significant ABD derived stroke volume for thermodilution stroke volume changes <20% was 0.75.

Discussion

We have examined an advanced transoesophageal echocardiographic technique for its accuracy and trend capability in estimating LV stroke volume during abdominal surgery. With reference to thermodilution, both ABD methods had poor accuracy in determining actual stroke volume, while they correctly identified approximately 75% of changes in stroke volume greater than 20%. The technique was applicable during operation in 80% of patients. The use of the methods required frequent probe manipulations and was associated with signal instability.

There are few methods currently available for monitoring stroke volume on a beat-to-beat basis. Stroke volume is commonly derived from thermodilution, which is invasive and gives only intermittent data. In contrast, acoustic quantification analyses continuously radiofrequency data and applied to transoesophageal echocardiography has the potential to accurately measure LV cavity area[5–10]. ABD algorithms for on-line calculation of LV volumes from single long-axis views are based on formulae recommended by the American Society of Echocardiography[11 12]. Recent transthoracic studies in a canine heart model[7] and in humans[8 9] have confirmed that ABD derived stroke volume from a single long-axis plane correlates closely with stroke volume

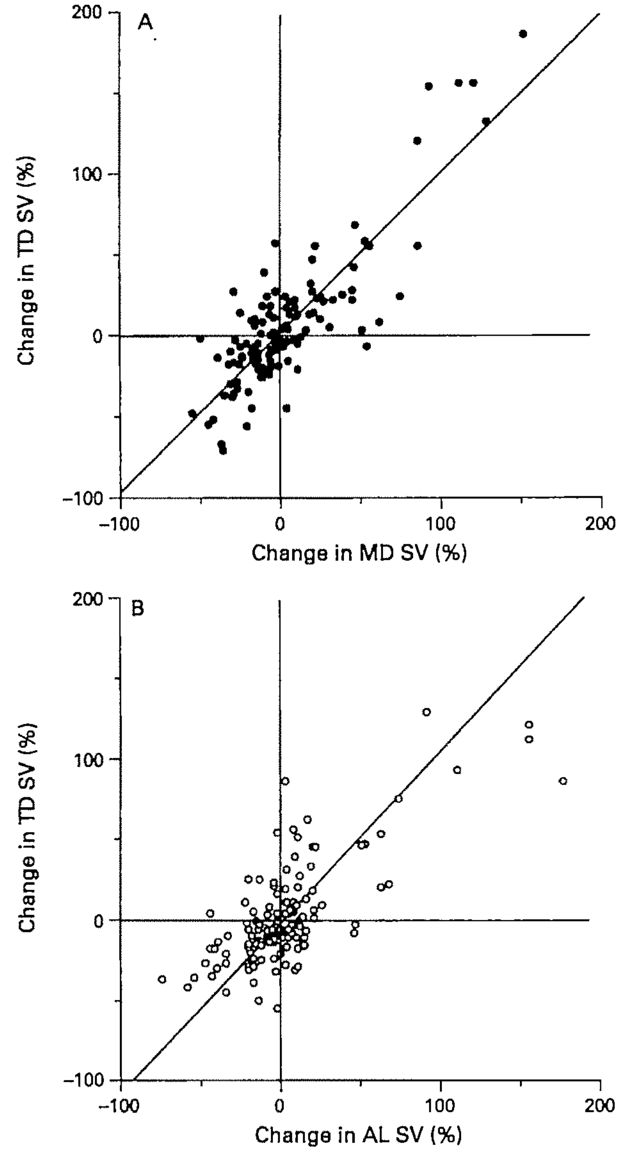


Figure 4 Linear regression of percentage changes in stroke volume (SV) obtained by (A) the multiple disc (MD) method ($y=1.0x+1.6$; $r=0.85$; SEE=32; $n=105$) and (B) the area–length (AL) method ($y=0.9x+2.0$; $r=0.79$; SEE=24; $n=105$) in relation to changes in thermodilution (TD) stroke volume.

obtained by other established methods. In common with this study, however, ABD methods consistently underestimated actual stroke volume and the limits of agreement were wide. A major drawback of this single-plane approach is the inability to see the apex of the left ventricle, which makes assessment of LV areas and axes by more than one plane a preferable technique for volume determination[13 14]. However, in the intraoperative situation, single-plane measurements provide practical advantages, because they allow rapid, serial estimates of cardiac filling and do not require data work up on various standard images.

While our results suggest that single-plane ABD methods reflect percentage changes in stroke volume and may be suitable for intraoperative trend analysis of stroke volume, they are disappointing with regard to measurement of stroke volume. Correlation of ABD methods with thermodilution showed better agreement in a previous transoesophageal study[4]. Katz and coworkers calculated regression coefficients from $r=0.74$ to $r=0.82$ for MD and AL derived stroke volume compared with thermodilution stroke volume, when a maximum of two data sets were obtained in each of 18 patients[4]. An excellent correlation between transthoracic ABD and the thermodilution technique was reported recently by Tardif and colleagues who measured cardiac output in critically ill patients[9]. In our study, the different approach and design may have contributed to the lower agreement between the ABD methods and thermodilution for several reasons. First, careful technical settings are critical to maintain precision of ABD data over hours. In our study, repeated manipulations of the probe were necessary as a result of surgical manoeuvres such as chest retraction or upper abdominal exploration. Artefacts and worsening of signal transmission with time may have occurred as a result of drying of the ultrasound transmission gel between the oesophageal mucosa and the transducer head. In addition, changes in end-diastolic LV volume required repeated adjustment of the limiting region of interest and played a role in the continuous performance of ABD methods. These factors may have contributed to the high variability in 16% of automated TOE data that required exclusion from further analysis.

Although there are several sources for ABD signal instability, we believe that a more important shortcoming of this monitoring technique is its lack of accuracy in true volume determination. This may become more prominent during major surgery involving various haemodynamic states that affect cardiac filling and contractility. Possibly, the error of a foreshortened long-axis image is potentiated by major changes in LV volume or heart rate that might result in significant variation in the selected imaging planes. Evaluation is required on the use of other single planes such as the standard four-chamber view which, in common with the two-chamber view, is reproducible and offers the potential for applying ABD methods. Another possible approach for intraoperative monitoring of stroke volume by acoustic quantification, which is based on the LV short-axis view, has been examined extensively by Gorcsan and colleagues[2 15]. This technique, however, most often requires intra-gastric positioning of the transducer probe and from our experience has a very high incidence of signal instability during abdominal surgery.

In summary, our results suggest that monitoring stroke volume with single-plane ABD methods does not hold promise as a clinically reliable technique because of the poor accuracy in computing stroke volume and signal instability, even during stable haemodynamic states, and its only moderate ability to detect acute changes in stroke volume during abdominal surgery.

References

1. Perez JE, Waggoner AD, Barzilai B, Melton HJ, Miller JG, Sobel BE. On-line assessment of ventricular function by automatic boundary detection and ultrasonic backscatter imaging. *Journal of the American College of Cardiology* 1992; 19: 313–320.
2. Gorcsan J III, Gasior TA, Mandarino WA, Deneault LG, Hattler BG, Pinsky MR. On-line estimation of changes in left ventricular stroke volume by transesophageal echocardiographic automated border detection in patients undergoing coronary artery bypass grafting. *American Journal of Cardiology* 1993; 72: 721–727.
3. Perrino AC, Luther MA, O'Connor TZ, Cohen IS. Automated echocardiographic analysis. Examination of serial

echocardiographic measurements. *Anesthesiology* 1995; **83**: 285–292.

4. Katz WE, Gasior TA, Reddy SCB, Gorcsan J III. Utility and limitations of biplane transesophageal echocardiographic automated border detection for estimation of left ventricular stroke volume and cardiac output determination. *American Heart Journal* 1994; **128**: 389–396.
5. Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *American Heart Journal* 1968; **75**: 325–334.
6. Goerke RJ, Carlsson E. Calculations of right and left ventricular volumes. Method using standard computer equipment and biplane angiocardiograms. *Investigative Radiology* 1967; **2**: 360–368.
7. Morrisey R, Siu SC, Guerrero JL, Weyman AE, Picard MH. Ventricular volume by echocardiographic automated border detection: On-line calculation without loss of accuracy. *Journal of the American College of Cardiology* 1993; **21**: 275A, 772-1.
8. Cao Q, Azevedo J, Snapper H, Schwartz S, Udelson J, Pandian N. Automated, on-line determination of left ventricular volumes and ejection fraction by acoustic quantification. *Journal of the American College of Cardiology* 1993: **21**: 275A, 772-2.
9. Tardif JC, Cao Q, Pandian NG, Esakof DD, Pollard H. Determination of cardiac output using acoustic quantification in critically ill patients. *American Journal of Cardiology* 1994; **74**: 810–813.
10. Bland JH, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
11. Cahalan MK, Ionescu P, Melton HE, Adler S, Kee LL, Schiller NB. Automated real-time analysis of intraoperative transesophageal echocardiograms. *Anesthesiology* 1993; **78**: 477–485.
12. Pearlman AS, Gardin JM, Martin RP, Parisi AF, Popp RL, Quinones MA, Stevenson JG, Schiller NB. Guidelines for physician training in transesophageal echocardiography: Recommendations of the American Society of Echocardiography Committee for Physician Training in Echocardiography. *Journal of the American Society of Echocardiography* 1992; **5**: 187–194.
13. Schnittger I, Fitzgerald PJ, Daughters GT, Ingels NB, Kantrowitz NE, Schwartzkopf A, Mead CW, Popp RL. Limitations of comparing left ventricular volumes by two-dimensional echocardiography, myocardial markers and cine-angiography. *American Journal of Cardiology* 1982; **50**: 512–519.
14. Hozumi T, Shakudo M, Shah P. Quantitation of left ventricular volumes and ejection fraction by biplane transesophageal echocardiography. *American Journal of Cardiology* 1993; **72**: 356–359.
15. Gorcsan J III, Lazar JM, Romand J, Pinsky MR. On-line estimation of stroke volume by means of echocardiographic automated border detection in the canine left ventricle. *American Heart Journal* 1993; **125**: 1316–1323.

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Patient-controlled sedation for cataract surgery using peribulbar block

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Summary

Patients undergoing cataract surgery using peribulbar block were allocated randomly to self-administer doses of either midazolam 0.1 mg or propofol 3.3 mg without a lock-out facility; in the control group the syringe was charged with saline, not as a placebo, but to "blind" the surgeon and the nurse observer. For midazolam and propofol, median doses were 2.54 (0.1–6.0) mg and 87.4 (0–145) mg, respectively. Patient-controlled sedation significantly reduced the level of anxiety, with median visual analogue anxiety scores in the midazolam, propofol and saline groups of 5 (0–38) mm, 5 (0–25) mm and 15 (0–92) mm, respectively ($P<0.05$). Some patients did not administer the sedative when available while others in the saline group would have benefited from anxiolytic drugs. While both drugs prevented an increase in heart rate, only midazolam prevented an increase in arterial pressure during surgery. (*Br. J. Anaesth.* 1996;**77**:370–374)

Key words

Hypnotics benzodiazepine, midazolam. Anaesthetic techniques, regional, peribulbar. Sedation, patient-controlled. Anaesthetics i.v., propofol. Surgery, ophthalmological. Age factors.

Cataract is predominantly a disease of old age[1 2]. The number of elderly patients in the UK, together with earlier referral of patients for treatment, is increasing the demand for cataract surgery[3 4], using day-care facilities[5 6].

Despite the availability of new anaesthetic drugs which allow rapid recovery, for example propofol, desflurane and sevoflurane, the use of local anaesthesia is increasing as it provides not only satisfactory operating conditions, but also advantages in terms of health economics[5]. A major disadvantage of local anaesthesia alone is anxiety, so that patients may be restless when immobility is required[7]. This may be overcome with anxiolytic drugs causing only minimal sedation. Unfortunately, a patient's response to a predetermined dose of a sedative drug may be unpredictable, particularly in the elderly where only relatively small doses are required[8–10].

An alternative would be patient-controlled sedation (PCS) which has been used successfully during surgery performed under local anaesthesia[11–14]. In early studies, the technique included an initial predetermined dose of the sedative drug before the patient took over which, by allowing the possibility of initial over sedation, may be a disadvantage. Recently, a modified patient-controlled analgesia pump (Graseby 3300, Watford, UK) without a lock-out period has been used to allow small doses of either propofol or midazolam to both initiate and maintain sedation[15]. The only restriction of access to the drug is the duration of injection of each dose, which was 5.4 s in these studies[15–17]. Patients use a much wider range of doses to achieve similar levels of psychomotor depression, with maintenance of verbal communication, than would be expected during physician administration.

We have evaluated this new method of total patient-controlled sedation in an elderly population undergoing cataract surgery during local anaesthesia.

Patients and methods

After obtaining approval from the Ethics and Research Committee (No. L94/1) and written informed consent, we enrolled 77 patients in the study. Exclusion criteria included age greater than 85 yr, clinical evidence of heart failure, severe pulmonary disease, sedative medication within the previous month, difficulty with language or communication, and poor vision in the nonoperated eye. Patients were allocated randomly to one of three groups by opening a sealed numbered enveloped containing the study group (120, 4-cm square labels, 40 each labelled midazolam, propofol, and placebo, were folded into four and mixed thoroughly in a box approximately 30 cm square by stirring and shaking, and were then taken out, placed in an envelope and numbered in the selected order). Three senior registrar anaesthetists and four ophthalmic surgeons of senior registrar or consultant status participated in the study. This was a single-blinded study with patients in the saline group informed that they were not receiving any sedation while the research nurse and the surgeons were blinded. We felt that it was inappropriate and unethical to allow patients to try to sedate themselves with saline.

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SEDATION EQUIPMENT

The use of the sedation pump (modified Graseby 3300, Watford, UK, no lock-out, infusion rate 200 ml h^{-1}) was explained to the patients. They were told that they may not feel the need to administer any drug. If they started to feel less relaxed or anxious they should press the button as often as required until they were no longer anxious and "felt good", and while they could press the button again whenever they felt they needed more drug, they should not attempt to become unconscious. The pump contained 30 ml of one of three solutions: 0.9% saline, with or without midazolam or propofol 10 mg (1%). It was set to administer 0.33-ml aliquots of solution, that is midazolam 0.1 mg or propofol 3.3 mg. A 21-gauge cannula was inserted into a vein in the forearm on the contralateral side to the arterial pressure cuff and connected to the patient-controlled sedation pump via a primed infusion cannula (standard intravascular monitoring catheter length 150 cm, internal diameter 1 mm). Patients who were allocated to the saline group were then informed that the pump did not contain any sedative drug and that they were the control group. The number of demands, and successfully administered boluses of drugs, were recorded.

PATIENT ASSESSMENT

Sedation

The level of *sedation* was graded before performing peribulbar block by an independent "blinded" research nurse using the following scale: (1) awake, anxious; (2) awake, not anxious; (3) sedated, speech slurred; and (4) eyes closed with appropriate response to verbal command[15]. Awake patients were asked by the nurse if they felt anxious. Intraoperative assessment was made by the operating surgeon.

Anxiety

Two hours after surgery, patients were reviewed by a different anaesthetist. The level of *anxiety* experienced in the intraoperative period by the patients was assessed retrospectively using a linear visual analogue scale (VAS) from 0 to 100 mm, where 0=feeling normal and not anxious and 100=extreme anxiety.

Psychomotor test

The use of the psychomotor test equipment was explained during an initial period of familiarization. Two ascending and descending readings were obtained for critical flicker fusion, a simple response time was repeated six times and a computerized digit span memory test was also applied. The psychomotor tests were performed by a nurse trained in the use of a portable notebook computer (Compaq Contura, Compaq Computer Corporation, Singapore). Baseline tests were performed before the start of each study and repeated 10, 30, 60 and 120 min after the end of surgery. It was not possible to apply the tests satisfactorily when the treatment pathway had started, because of the speed of events, changing conditions and limited access to the patients.

MONITORING

The electrocardiogram (Cardiorecorder 364 AM, UK), heart rate and arterial oxygen saturation (Sp_{O_2}) (Novametric 515 A, USA) were monitored continuously together with intermittent measurements of non-invasive arterial pressure (Dinamap Criticon A 45, UK). Baseline readings were recorded before sedation and repeated at 5-min intervals thereafter, including the phase I recovery area after surgery.

PERIBULBAR BLOCK

All patients, whether receiving saline, sedation or those not taking sedation, indicated that they were ready for the block when assessed within 5–10 min after connection of the sedation apparatus, which in the saline group was there to blind the observers. After the research nurse had assessed the level of sedation, which took approximately 2–4 min, a peribulbar local anaesthetic block was performed on the operated eye using 8 ml of a mixture of equal volumes of 0.5% bupivacaine and 2% lignocaine to which 150 iu of hyaluronidase had been added. A Honan balloon was applied for 20 min to facilitate spread of the local anaesthetic into the muscle cone and subsequently to reduce intraocular pressure. Additional local anaesthetic was administered when required to ensure satisfactory block.

PROCEDURE

After transfer to the operating theatre, the surgical field was prepared. Oxygen was delivered at 6 litre min^{-1} by a cannula placed close to the nostrils under the drapes. The PCS apparatus was positioned near the patient's feet under the surgical drapes but easily accessible to the anaesthetist. Before surgery, the surgeon, who was blinded to the sedative technique, assessed the degree of ocular movement using a recognized scale[18].

In the intraoperative period, patients maintained their own level of anxiolysis and the anaesthetist was present throughout. The surgeon ascertained that patients were not over sedated by maintaining verbal contact. At the end of the operation, the surgeon recorded the quality of the local anaesthesia and also the patient's cooperation during surgery. Assessment of cooperation was left to the discretion of the surgeon and was considered good if the patient responded appropriately to his request and did not move unexpectedly during the procedure. Sedation was then discontinued and the duration of use of the sedation pump and surgery were recorded.

Patients were then transferred to the recovery unit (phase I) where they remained until completion of the study. After step down (phase II), patients were reviewed by a second anaesthetist before discharge.

STATISTICAL ANALYSIS

Analysis of variance (ANOVA) was applied to normally distributed data. The difference between the highest systolic and diastolic pressures and heart rate and baseline pressure in each patient were compared between groups using one-factor ANOVA. Within each group, comparison with baseline was made using Student's paired *t* tests with Bonferroni's correction. Sedation scores were compared using chi-square analysis and the median anxiety scores were compared using the Mann–Whitney *U* test. The results of the psychometric tests were analysed using

Friedman's two-way analysis of variance for repeated measurements. $P<0.05$ was considered statistically significant.

Results

Two patients were removed from the study; one became over sedated with midazolam and its effects were reversed with flumazenil 0.5 mg i.v. before the local anaesthetic block was performed; the other in the non-sedated group, suffered a posterior capsular tear with vitreous loss.

There were no significant differences in patient characteristics between the groups (table 1) and no differences in duration of surgery, quality of local anaesthesia (table 2) or ocular muscle paralysis. In one patient in the midazolam group and two in the propofol group, local anaesthetic action wore off during surgery and was supplemented with 1% topical amethocaine. Cooperation of the patients, assessed by the surgeon, was good, except for one non-sedated patient, three patients in the midazolam group and one in the propofol group (table 2).

The median total doses of midazolam and propofol were 2.54 mg and 87.4 mg, respectively (table 2). Three patients in the propofol group did not use the pump but their anxiety scores were 0–6 mm on the VAS. Three patients in the midazolam group fell asleep during surgery but were awakened immediately by verbal communication, without distress or restlessness, and with appropriate responses to instructions.

Sedation scores before performing peribulbar block were grouped as inadequate (group 1) and adequate (groups 2–4). There were significantly more patients in the saline group who were inadequately sedated compared with those in the midazolam and propofol groups (table 3). There was no significant difference in the degree of sedation between the midazolam and propofol groups and only two patients were considered retrospectively to have used too little sedation.

Overall, the non-sedated group was significantly more anxious during surgery. They had a median VAS of 15 mm compared with 5 mm in the midazolam and propofol groups (table 3). However, seven (27%) patients in the non-sedated group when assessed after surgery had a VAS anxiety score of 0 mm.

The results of the psychomotor tests, which were performed before and after the procedure, were not significantly different either between the three groups or within each group (table 4). Three patients in the midazolam group had complete amnesia for intraoperative events.

Only one patient (in the midazolam group) developed an arterial saturation of less than 90% for more than 1 min. This occurred 20 min after initiation of sedation while breathing air. Saturation improved immediately when the patient was asked to inhale a few deep breaths and remained greater than 92% throughout the remainder of the study.

There were no significant differences in mean control systolic and diastolic arterial pressures, which were 148.8 (SD 17.3) mm Hg and 86.2 (21.5) mm Hg in the placebo group, 157.5 (13.9) mm Hg and 85.7 (11.4) mm Hg in the midazolam group, and

Table 1 Patient characteristics for the three groups (mean (SD or range) or number)

	Non-sedated group (n=26)	Midazolam group (n=24)	Propofol group (n=25)
Age (yr)	70 (52–85)	70.3 (44–85)	67 (45–82)
Weight (kg)	71 (15.3)	70.1 (13.4)	70 (14.8)
Sex (M:F)	13:13	12:12	11:14
ASA (I/II/III)	13/13/0	14/10/0	9/16/0

Table 2 Duration of surgery and patient-controlled sedation (PCS) (mean (SD), total amount of drug used (median (range)), number of patients who could not recall operative events and quality of anaesthesia and co operation of the patients in the three groups, no significant differences between groups

	Non-sedated group (n=26)	Midazolam group (n=24)	Propofol group (n=25)
Duration of surgery (min)	43.9 (23.5)	40.1 (14.4)	42.6 (15.2)
Duration of PCS use (min)	0	93.3 (33.4)	89.6 (20.1)
Amount of drug used before block (mg)	0	1.62 (0.1–4.8)	40.1 (0–145)
Total amount of drug used (mg)	0	2.54 (0.1–6.0)	87.4 (0–195)
Complete amnesia during surgery			
Yes	0	3	0
No	26	21	25
Quality of local anaesthesia			
Good	25	23	23
Poor	1	1	2
Cooperation of patient during surgery			
Good	25	21	24
Bad	1	3	1

Table 3 Assessment of sedation and anxiety. Degree of sedation before peribulbar block and anxiety experienced during surgery (retrospective) using a visual analogue scale ((VAS) of 0–100 mm). Sedation state was analysed using the chi-square test and anxiety score using the Mann-Whitney U test. $^*P < 0.05$

	Non-sedated group (n=26)	Midazolam group (n=24)	Propofol group (n=25)
Sedation score			
1	9	2	0
2	17	15	19
3	0	6	5
4	0	1	1
Inadequate (1)	9*	2	0
Adequate (2+3+4)	17*	22	25
Anxiety score (mm) (median (range))	15 (0–92)*	5 (0–38)	5 (0–25)

Table 4 Psychometric studies. Effect of midazolam, propofol and placebo on psychometric tests before sedation and after surgery (mean (SD)). SRT = Simple response time, CFF = Critical flicker fusion, DS = Digital span memory test (maximum number of digits scored correctly). Data were compared using two-way analysis of variance. No significant differences between groups

			Time after surgery (min)			
Group	*n*	Before sedation	10	30	60	120
SRT (ms)						
Placebo	26	331 (104)	368 (183)	363 (157)	353 (140)	367 (185)
Midazolam	24	335 (74)	477 (456)	447 (472)	344 (123)	350 (133)
Propofol	25	375 (158)	535 (617)	346 (112)	352 (114)	334 (87)
CFF (Hz)						
Placebo	26	34.0 (3.0)	34.1 (3.0)	34.0 (3.4)	34.4 (3.1)	33.8 (3.4)
Midazolam	24	34.0 (2.3)	34.3 (3.8)	33.9 (4.3)	35.3 (3.8)	33.9 (2.2)
Propofol	25	34.3 (2.9)	34.0 (2.1)	34.6 (2.7)	34.0 (2.4)	35.0 (2.9)
DS (No.)						
Placebo	26	5.0 (1.3)	5.0 (1.1)	5.1 (1.4)	5.4 (1.4)	5.3 (1.2)
Midazolam	24	5.5 (1.1)	4.5 (1.1)	5.2 (1.0)	5.0 (1.0)	5.0 (1.3)
Propofol	25	5.8 (1.0)	5.2 (1.1)	5.2 (1.1)	5.6 (1.0)	5.6 (1.3)

150.1 (18.8) mm Hg and 86 (12.1) mm Hg in the propofol group. In the saline and propofol groups there were significant peak increases of 14.6 and 9.4 mm Hg in mean systolic pressure ($P<0.05$ in each). In contrast, in the midazolam group, mean arterial pressure changed by only 2.4 mm Hg (ns). In all groups arterial pressure returned to near control values by the end of the procedure. There were no significant changes in mean diastolic pressure.

One non-sedated patient was restless and his systolic and diastolic arterial pressures increased to 200 and 120 mm Hg, respectively, and were restored to normal control levels with labetalol (total dose 30 mg i.v.). The patient was not known to suffer from hypertension but was extremely anxious during surgery, with a retrospective anxiety score of 92 mm on the VAS.

Mean control heart rates were 73.2 (10.8), 72.4 (11.4) and 74.4 (11.1) beat min^{-1} in the saline, midazolam and propofol groups, respectively. There were no significant changes in heart rate throughout the study in the midazolam and propofol groups, and although the unsedated group demonstrated a significant peak increase in mean heart rate during surgery, it was only 4.2 beat min^{-1} and therefore not clinically important. Heart rate exceeded 90 beat min^{-1} in approximately 33% of patients.

Discussion

We have demonstrated that elderly patients can use patient-controlled sedation during cataract surgery to induce and maintain anxiolysis and conscious sedation with minimal drowsiness (table 3).

The term sedation used in the study dose not refer to the degree of drowsiness but rather describes a state of anxiolysis. When patients feel very relaxed, they can become very drowsy but verbal communication is retained. This method of sedation is as safe as other methods and may have advantages over other techniques where an anaesthetist or other practitioner induces and maintains sedation [7–9]. Both midazolam and propofol were effective in obtunding an increase in heart rate during surgery, which occurred in the non-sedated group, but only midazolam prevented an increase in arterial pressure, which confirms a previous report in patients undergoing cataract surgery[7].

Clearly sedation is not required in all patients undergoing cataract surgery with local anaesthesia but although the 26 patients in the control group managed without sedation, some were very anxious, as demonstrated retrospectively by the VAS anxiety scores. All patients in the midazolam group received some drug even though their median anxiety score (VAS) was only 5 mm (range 0–38 mm) (table 3). In contrast, three patients in the propofol group with VAS anxiety scores less than 6 mm did not receive any drug and seven (27%) patients in the non-sedated group had an anxiety score of 0 mm during surgery. Therefore, 10 of 75 patients (13%) did not require any sedation and for several other patients, drug consumption was minimal (table 2). Thus as the need for sedation is unpredictable and clearly there is no requirement for routine use, a case may be made for demand sedation in all patients. In these situations security and confidence are provided by patients' knowledge of the immediate availability of sedation should they become acutely anxious[15]. Moreover, intervention with sedative drugs administered i.v. by anaesthetists or surgeons can be disastrous when surgery has started. This has been demonstrated in a study where administration of infusions of either midazolam or propofol by anaesthetists during cataract surgery, to achieve a predicted level of sedation with cooperative dysarthria, caused loss of airway patency in some patients[19].

In one patient in the midazolam group, verbal communication was lost before peribulbar block was performed because of "stacking" of doses to a total of more than 5 mg. This is predictable in some elderly patients with slow circulation times. It is caused by the slow onset time of midazolam[20] and is reversed easily with flumazenil. A similar problem during cataract surgery has been reported after administration of midazolam 20 $\mu g\ kg^{-1}$ i.m. where 33% of patients fell asleep[8].

The absence of a formal lock-out time implies that the time between successful demands was only 5.4 s, that is the duration of injection of each bolus. In previous studies using the same demand sedation system in healthier younger patients, none become over sedated[15]. In this study, no patient receiving propofol, which has a shorter onset time[14,21], became over sedated. Thus although midazolam is very effective at relieving anxiety and suppressing a cardiovascular response to surgery, in elderly patients small doses and a lock-out time during patient-controlled sedation are to be recommended.

In terms of respiratory depression, our sedation technique compared favourably with other studies. For example, apnoea was reported in five (16.1%) patients who received fentanyl 0.5 μg kg^{-1} and midazolam 0.0015 mg kg^{-1} i.v.[9]. Both midazolam and propofol depress hypoxic ventilatory drive in humans[22 23] and although our method of sedation appears to be better than others[9 10], we recommend routine use of supplementary oxygen whenever possible, as the alternative of deep breathing may cause coughing.

Three (12.5%) patients in the midazolam group were completely amnesic for all surgical events. This is less than in a previous study where premedication with temazepam 10 mg orally combined with midazolam in a mean total dose 1.41 mg for cataract surgery resulted in an incidence of amnesia of 29.4%[19].

There were no significant differences in the results of the psychomotor tests before and after surgery which, on average, lasted 40 min (table 2). Because of clinical constraints, the group of psychomotor tests could not be reapplied in a valid way until the postoperative period. Patients administered only small amounts of either midazolam (median 2.54 mg) or propofol (mean 87.4 mg) (table 2), approximately 50% of the dose before peribulbar block and most of the remainder at the beginning of surgery. As the psychomotor tests were performed after the end of the procedure, that is on average more than 50 min after the last dose of either drug, it is not surprising that potential small differences between the drugs were not detected. Also, in another study where drugs were administered in predetermined doses by an anaesthetist, recovery measured by the response time was similar for both midazolam and propofol[24]. Midazolam is the recommended anxiolytic drug for use by non-anaesthetically trained practitioners[25] and has the advantage of the possibility of immediate reversibility of effect by flumazenil. Nevertheless, patients should be supervised continuously by a competent person, as has been recommended recently for propofol[26].

Acknowledgements

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References

1. De Natale R, Flammer J. Lens opacity: a population study. *International Ophthalmology* 1992; **16**: 1–5.
2. Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam eye study. *Ophthalmology* 1992; **99**: 546–552.
3. Ferguson JA, Goldacre MJ, Henderson J, Bron AJ. Ophthalmology in the Oxford region: Analysis of time trends from linked statistics. *Eye* 1991; **5**: 379–384.
4. Batterbury M, Khaw PT, Hands R, Elkington AR. The cataract explosion: The changing pattern of diagnoses of patients attending an ophthalmic outpatient department. *Eye* 1991; **5**: 369–372.
5. Strong NP, Wigmore W, Smithson S, Rhodes S, Woodruff G, Rosenthal AR. Daycase cataract surgery. *British Journal of Ophthalmology* 1991; **75**: 731–733.
6. Watts WT, Pearce JL. Day-case cataract surgery. *British Journal of Ophthalmology* 1988; **72**: 897–899.
7. Gobeaux D, Sardnal F. Midazolam and flumazenil in ophthalmology. *Acta Anaesthesiology Scandinavia* 1990; **34** (Suppl. 92): 35–38.
8. Virkkila MEJ, Ali-Melkkila TM, Kanto JH. Premedication for outpatient cataract surgery: a comparative study of intramuscular alfentanil, midazolam and placebo. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 559–563.
9. Chung F, Cheng DC, Seyone C, Dyck BJ. A randomised comparison of midazolam and diazepam injectable emulsion in cataract surgery. *Canadian Journal of Anaesthesia* 1990; **37**: 528–33.
10. Forrest JB, Lam L, Woo J, Rifkind A. Oxygen desaturation in elderly patients during cataract surgery. *Canadian Journal of Anaesthesia* 1990; **37**: S50.
11. Osborne GA, Rudkin GE, Curtis NJ, Vickers D, Cracker AJ. Intra-operative patientcontrolled sedation. Comparison of patient-controlled sedation with anaesthetist administered midazolam and fentanyl. *Anaesthesia* 1991; **46**: 553–556.
12. Park WK, Watkins PA. Patient-controlled sedation during extradural anesthesia. *Anesthesia and Analgesia* 1991; **72**: 304–307.
13. Rudkin GE, Osborne GA, Curtis NJ. Intra-operative patient-controlled sedation. *Anaesthesia* 1991; **46**: 90–92.
14. Rudkin GE, Osborne GA, Finn BP, Jarvis DA, Vickers D. Intra-operative patientcontrolled sedation. Comparison of patient-controlled propofol with patient-controlled midazolam. *Anaesthesia* 1992; **47**: 376–381.
15. Cook LB, Lockwood GG, Moore CM, Whitwam JG. True patient-controlled sedation. *Anaesthesia* 1993; **48**: 1039–1044.
16. Whitwam JG, Wang C. Sedation and sedoanalgesia. In: Whitwam JG, ed. *Day-case Anaesthesia*. Oxford: Blackwell Scientific, 1994; 262–274.
17. Cook LB, Whitwam JG. Patient controlled sedation. In: Whitwam J, ed. *Day-case anaesthesia*. Oxford: Blackwell Scientific, 1994; 275–288.
18. Mein J, Harcourt B. Ocular movements. In: Mein J, Hartcourt B, eds. *Diagnosis and Management of Ocular Motility Disorders*. Oxford: Blackwell Scientific, 1986; 64–86.
19. Salmon JF, Mets B, James MF, Murray AD. Intravenous sedation for ocular surgery under local anaesthesia. *British Journal of Ophthalmology* 1992; **76**: 598–601.
20. Reves JR, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam pharmacology and uses. *Anesthesiology* 1985; **62**: 310– 324.
21. Sebel PS, Lowdon JD. Propofol: A new intravenous anesthetic. *Anesthesiology* 1989; **71**: 260–277.
22. Alexander CM, Gross JB. Sedative doses of midazolam depress hypoxic ventilatory responses in humans. *Anesthesia and Analgesia* 1988; **67**: 377–382.
23. Blouin RT, Seifert HA, Babenco HD, Conard PF, Gross JB. Propofol depresses the hypoxic ventilatory response during conscious sedation and isohypercapnia. *Anesthesiology* 1993; **79**: 1177–1182.
24. Polster MR, Gray PA, O'Sullivan G, McCarthy RA, Park GR. Comparison of sedative and amnesic effects of midazolam and propofol. *British Journal of Anaesthesia* 1993; **70**: 612–616.
25. Royal College of Surgeons of England. Report of working party. Guidelines for sedation by non-anaesthetist. London: Royal College of Surgeons of England, 1993.
26. Thorpe SJ, Balkvishnan VR, Cook LB. Observations on patient-controlled administration of propofol. *British Journal of Anaesthesia* 1996; **76**: 579P.

British Journal of Anaesthesia 1996;77:375–380

LABORATORY INVESTIGATIONS

Synergistic interactions between midazolam and alfentanil in isolated neonatal rat spinal cord

J. FENG AND J. J. KENDIG

Summary

Benzodiazepines, which may themselves have analgesic properties, display complex interactions with opioids. This study was designed to investigate the effects of midazolam on nociceptive neurotransmission in isolated neonatal rat spinal cord, and the interactions between midazolam and alfentanil. Slow ventral root potentials (sVRP) were recorded from a lumbar root of spinal cords isolated from 1–7-day-old rats and superfused at 27–28 °C. Midazolam (35 nmol litre^{-1} to 15 μmol litre^{-1}) significantly ($P<0.05$) depressed sVRP area in a concentration-dependent manner. Midazolam depression was antagonized by flumazenil, bicuculline and naloxone. Midazolam and alfentanil interacted synergistically, as determined by a combination index of less than 1. Midazolam blocked the rebound hyperexcitability observed when alfentanil was reversed by naloxone. The results of the study are relevant to benzodiazepine–opioid analgesia and to the effectiveness of benzodiazepines in mitigating the development of opioid tolerance and dependence. (*Br. J. Anaesth.* 1996;**77**:375–380)

Key words

Hypnotics benzodiazepine, midazolam. Analgesics opioid, alfentanil. Spinal cord. Rat. Pharmacology, synergism.

A benzodiazepine combined with an opioid analgesic is commonly used for i.v. anesthesia. There is controversy on whether or not benzodiazepines are analgesics[1–4]; given spinally, their effects appear to be analgesic[1] but systemically their sedative and anxiolytic properties may interfere with the assessment of pain[5]. Complex interactions between benzodiazepines and opioids have been reported with respect to analgesia [2 6–8], sedation–hypnosis[8–10] and development of opioid tolerance[11–13]. We have previously reported the effects of μ opioids on nociceptive neurotransmission in isolated neonatal rat spinal cord[14–16]. In response to stimulation of a lumbar dorsal root, a slow ventral root potential (sVRP) lasting 20–40 s can be recorded at the corresponding ipsilateral ventral root. The sVRP is related to nociception by several criteria. The fully developed sVRP requires C-fibre activation[17]. Both NMDA and neurokinin receptors are involved in sVRP generation[18], and both are linked to pain neurotransmission. An sVRP can be evoked by true noxious stimulation[19 20]. The sVRP is highly sensitive to analgesic agents, including opioids[14] and α_2 adrenoceptor agonists[21].

The sVRP is depressed by the benzodiazepine diazepam[22]. This study was designed to examine the effects of the benzodiazepine midazolam on the sVRP, and to investigate the interactions between midazolam and the μ opioid alfentanil.

Materials and methods

After obtaining approved from Stanford's Animal Care and Use Committee, newborn (1–6-day-old) Sprague–Dawley rat pups were anaesthetized with enflurane and decapitated. The spinal cord from the mid-thoracic to sacral level was removed rapidly and perfused at a rate of 4 ml min^{-1} with artificial cerebrospinal fluid (ACSF) at 27–28 °C, equilibrated with 95% oxygen–5% carbon dioxide, pH 7.3–7.4. This temperature is physiological for rats of this age when not in close contact with the mother. The ACSF consisted of (mmol litre^{-1}): NaCl 123, KCl 5, NaH_2PO_4 1.2, $MgSO_4$ 1.3, $NaHCO_3$ 26, $CaCl_2$ 2, glucose 30. This concentration of glucose was chosen because it increases viability in a more demanding version of this preparation, the spinal cord with brainstem attached in which spontaneous fictive respiratory discharges are maintained[23].

Suction electrodes were arranged to stimulate a lumbar dorsal root and record from the corresponding ipsilateral ventral root. Stimuli were single square wave pulses of 0.2 ms in duration. Stimulus intensity was adjusted to be supramaximal for eliciting the sVRP, and frequency was maintained at 0.02 Hz throughout the study. Responses were digitized, averaged in groups of 5 and stored for later analysis.

Controls for each experiment were the mean of 4–7 averaged responses obtained 30 min before administration of drug. Intermittently throughout the study, time-matched control experiments were carried out. Controls for individual drug experiments and time-matched controls over the duration of a typical experiment were within the range 95–105% of control means. Drugs obtained as pure compound were made up as stock solutions in distilled water,

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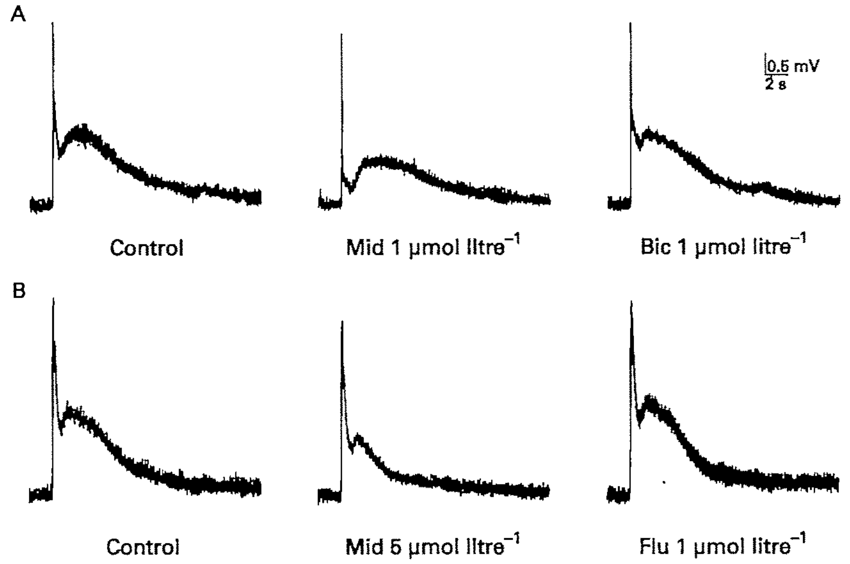

Figure 1 Examples of the effects of midazolam (Mid) on the slow ventral root potential (sVRP). A: Midazolam 1 μmol litre^{-1} depressed the sVRP and the depression was antagonized by the GABA$_A$ antagonist bicuculline (Bic) 1 μmol litre^{-1}. B: Midazolam 5 μmol litre^{-1} depressed the sVRP and the depression was antagonized by the benzodiazepine antagonist flumazenil (Flu) 1 μmol litre^{-1}.

diluted to the desired concentration in ACSF and applied to the cord in the perfusate for 30–60 min. The pH of the solution of diluted drug was 7.3–7.4. In single-drug studies, each preparation was exposed for 30 min to a single concentration of one agent, then to either drug-free ACSF or an antagonist for 1 h. In combination studies, a fixed concentration of one agent was co-administered with one of a range of concentrations of the other for 30 min; again each preparation was exposed to only one concentration of the second agent.

sVRP was quantified as the area under the curve. In a more detailed analysis, the sVRP was divided into an early area, maximally sensitive to NMDA antagonists, from 80 to 440 ms, and a late area, probably mediated via metabotropic receptors of more than one type, from 2.5 to 7.8 s[16]. Results were normalized to control. Slopes of dose–response curves were calculated by linear regression analysis of the log dose–response curve. To test for synergism against additive interactions of midazolam and alfentanil, the combination index (CI) was calculated from median-effect plots for each agent and compared with the predicted value for additivity[24].

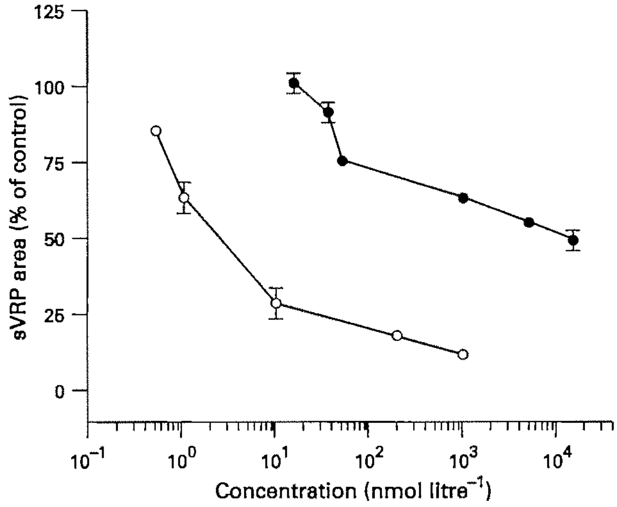

Figure 2 Dose–response curves for alfentanil (○) and midazolam (●) depression of the slow ventral root potential (sVRP). Midazolam exerted significant depressant effects at concentrations of 35 nmol litre^{-1} and above. Midazolam was less potent than alfentanil on an equimolar basis and its maximum depressant effect was much less. Data points are mean (SEM) of 4–13 experiments, in each of which the preparation was exposed to a single concentration of one of the agents.

Results

MIDAZOLAM DEPRESSION OF SVRP

Midazolam, in concentrations of 35 mmol litre^{-1} to 15 μmol litre^{-1}, significantly ($P<0.05$ to $P<0.0001$) depressed sVRP area; examples are shown in figure 1. Depression of the entire sVRP area by midazolam was concentration-dependent (fig. 2). As we have reported previously, alfentanil also depressed the sVRP area more potently than midazolam (fig. 2). Although it appeared that the slope of the midazolam concentration–response curve was shallower than that for alfentanil (midazolam slope −15.62 (SEM 2.375), alfentanil −20.92 (4.622) by linear regression analysis), the difference was not significant.

In previous studies we have shown that both μ and κ opioids selectively depressed the slower late phase of the sVRP compared with a relatively fast region sensitive to NMDA receptor antagonists[14 16]. The same was not true for midazolam. Midazolam up to 1 μmol litre^{-1} exerted similar effects on the early (80–440 ms) and late (2.5–7.8 s) phases of the response (fig. 3). At higher concentrations, however, an apparently biphasic effect of midazolam on the early phase was revealed; 5 and 15 μmol litre^{-1} continued to exert a concentration-dependent depressant effect on the late phase but appeared to be less effective than lower concentrations in depressing the early phase (fig. 3). This biphasic effect contributed to the shallow dose–response relationship for overall midazolam depression, and to the modest maximum depressant effect.

MIDAZOLAM–ALFENTANIL INTERACTIONS

Interaction between midazolam and alfentanil was examined by calculating a combination index (CI)[24]. The equation for the CI (eqn (1)) was solved in two ways: for CI using actual concentrations of agents in

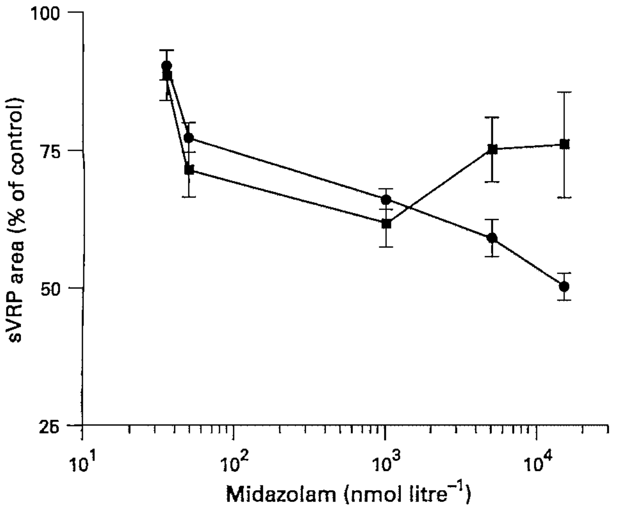

Figure 3 Effects of midazolam on the early area of the slow ventral root potential (sVRP) maximally sensitive to NMDA antagonists, 80–440 ms after the stimulus (NMDA area, ●) compared with effects on the slower metabotropic receptor-mediated component of the sVRP (late area, ●). The effects of midazolam on the two components were similar at concentrations of up to 100 nmol litre^{-1}. Above 100 nmol litre^{-1}, the effectiveness of midazolam on the early area decreased while the later area continued to decline. Data points are mean (SEM) of 5–9 experiments, in each of which the preparation was exposed to a single concentration of midazolam.

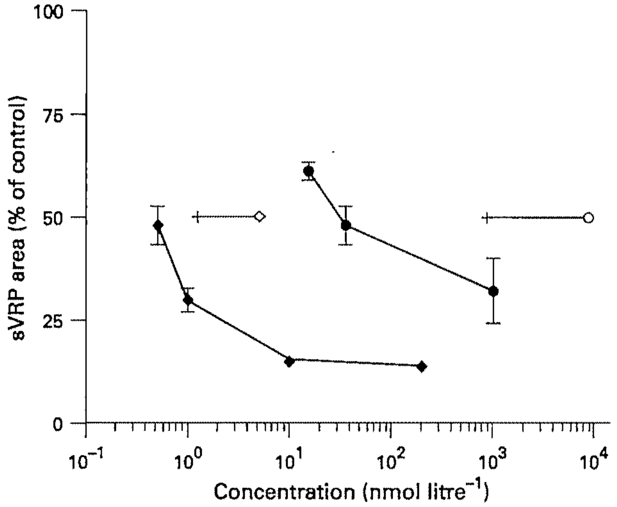

Figure 4 Concentration–effect plots determined when alfentanil was fixed at 0.5 nmol litre^{-1} and midazolam was varied (●) and when midazolam was fixed at 35 nmol litre^{-1} and alfentanil was varied (♦). These actual combinations were compared with the predicted median effective concentrations of midazolam in combination with alfentanil 0.5 nmol litre^{-1} (○) and of alfentanil in combination with midazolam 35 nmol litre^{-1} (◇), respectively, under an assumption of additivity. Data points from the actual combinations are mean (SEM) of 4–6 experiments, each preparation exposed to one mixture. Predicted concentrations were derived from equation (1) with the value for CI fixed at 1. Predicted concentrations use median effect plots derived from transformed dose–response curves. Horizontal error bars=95% confidence limits of the regression line drawn through the median effect plots. Both combinations were more effective than predicted by additivity; midazolam and alfentanil interacted synergistically to depress sVRP.

combination and the concentration of each agent required to produce a given effect by itself; and for the predicted concentration of one agent required to be added to a known concentration of the other to produce a median effect assuming additivity (CI=1). The latter was then plotted on a graph of the actual combination drug effects (fig. 4),

$$\mathrm{CI}=C_{A}/A+C_{M}/M+(C_{M}\times C_{A}/MA) \qquad (1)$$

where CI=combination index, C_A and C_M= concentrations of alfentanil and midazolam given in combination to produce a given level of effect, and A and M=concentrations of each agent separately required to produce the same level of effect. A CI value of 1 indicates additivity, less than 1 synergism and greater than 1 antagonism.

When CI was determined with known concentrations of agents to produce a given effect, values ranged from 0.1 to 0.5, depending on the effect level chosen. This result indicates that interactions between alfentanil and midazolam were synergistic. Synergism was confirmed by the finding that midazolam 15 nmol litre^{-1}, a concentration with no effect on sVRP, significantly potentiated the depressant effect of alfentanil (fig. 4). When CI was assigned a value of 1 under an assumption of additivity, and the predicted concentration of midazolam or alfentanil required to produce the median effect in combination with the other drug was calculated, the actual curves for midazolam–alfentanil combinations were shifted markedly to the left from the points predicted by the assumption of additivity (fig. 4).

RECEPTOR SPECIFICITY OF MIDAZOLAM AND ALFENTANIL ACTIONS

Midazolam is presumed to act at the benzodiazepine receptor site on the GABA$_A$ receptor. The benzodiazepine antagonist flumazenil and the GABA$_A$ antagonist bicuculline were examined for their own effects and for ability to antagonize the effects of midazolam. Both agents increased sVRP area at concentrations of 500 µmol litre^{-1} and above (fig. 5). Both flumazenil and bicuculline antagonized the effect of low (50 nmol litre^{-1}) concentrations of midazolam at concentrations at which they themselves did not increase sVRP area (50 nmol litre^{-1}); at higher midazolam concentrations (1µmol litre^{-1}), effective antagonism was observed only with higher antagonist concentrations, in the ranges in which the antagonists themselves increased sVRP area (1 µmol litre^{-1}).

There was unidirectional cross-antagonism between opioid receptor antagonist and the benzodiazepine receptor agonist. The effects of midazolam 1 µmol litre^{-1} were antagonized by the non-specific opioid antagonist naloxone at a concentration that itself had no significant effect on the sVRP (200 nmol litre^{-1}). The GABA$_A$ antagonist bicuculline (200 nmol litre^{-1}) did not antagonize the effects of alfentanil (200 nmol litre^{-1}).

MIDAZOLAM EFFECTS ON OPIOID-INDUCED HYPER-RESPONSIVENESS

We have observed previously that naloxone, given after µ opioids, precipitated an increase in sVRP area to levels above pre-drug controls[14 15]. Midazolam 35 and 1000 nmol litre^{-1}, but not 15 nmol litre^{-1} blocked this increase (fig. 6). Bicuculline 200 nmol litre^{-1} did not affect the increase, suggesting that the latter was not mediated via disinhibition at GABA$_A$ receptors (fig. 6).

Discussion

Midazolam itself depresses spinal nociceptive neurotransmission, as measured by changes in the

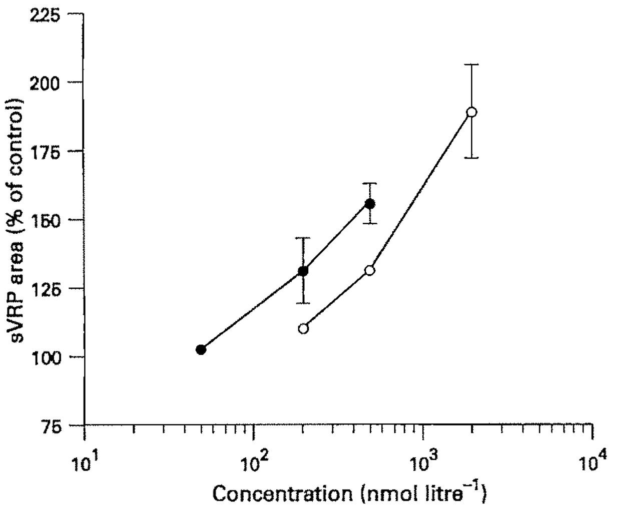

Figure 5 Both flumazenil (●) and bicuculline (○) alone increased sVRP area. The increase was significant ($P<0.05$) at concentrations of 500 nmol litre^{-1} and above for each agent. Data points are mean (SEM) of 4–6 individual experiments, each preparation exposed to a single concentration of one of the agents.

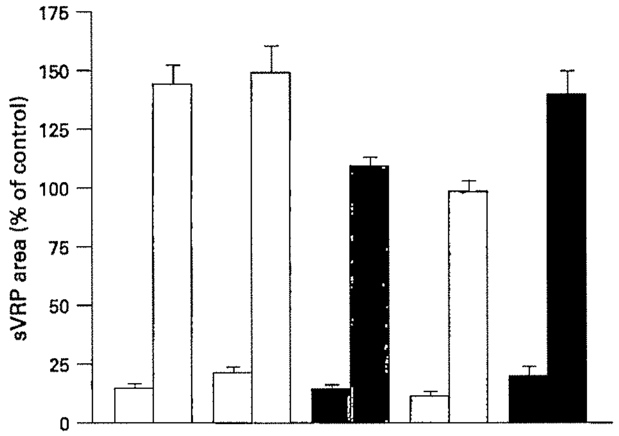

Figure 6 Midazolam prevented the rebound hyperresponsiveness observed when alfentanil 200 nmol litre^{-1} was followed by naloxone 200 nmol litre^{-1}. In each pair of bars, the agonist effect is on the left, followed by antagonist on the right. Midazolam 15 nmol litre^{-1} co-administered with alfentanil was not effective, but 35 nmol litre^{-1} and 1 μmol litre^{-1} were. Pale grey=alfentanil followed by naloxone; open bars=alfentanil and midazolam 15 nmol litre^{-1}, with and without naloxone; dark grey=alfentanil and midazolam 35 nmol litre^{1}, with and without naloxone; medium grey =alfentanil and midazolam 1 μmol litre^{-1}, with and without naloxone; solid bars=alfentanil and bicuculline 200 nmol litre^{-1}, with and without naloxone. Data are mean (SEM) of 5–14 individual experiments.

nociceptive-related slow ventral root potential. The effect, however, is complicated by a biphasic concentration–response curve for the early NMDA receptor-mediated component of the sVRP. The significance of this with respect to analgesia is unclear, although it may be related to a plateau effect and contribute to the very high midazolam doses required for immobility in response to a noxious stimulus (J. Mandema, personal communication). Its implication for midazolam–alfentanil interaction is discussed below.

In an experimental animal model of pain, flumazenil and bicuculline attenuated analgesia produced by subarachnoid administration of midazolam in the lumbar region[1]. Analgesia and a decrease in sVRP area thus result from the action of midazolam on the benzodiazepine site of a $GABA_A$ receptor population in spinal cord. Naloxone also antagonized the analgesic effect of both alfentanil and midazolam in animal models[25,26], indicating that some benzodiazepine effects may be mediated via an opioid pathway in spinal cord. GABA antagonists failed to antagonize opioid effects in animal models[1,25]. The results of our study are consistent with these findings, and suggest that the opioid receptor is downstream from the benzodiazepine receptor in the pathway. Benzodiazepines may act by enhancing release of endogenous opioids or potentiating their effects, or both. In light of marked benzodiazepine potentiation of exogenous opioid agonist effects, the latter possibility seems likely.

The effectiveness of flumazenil and bicuculline as antagonists confirms the reasonable assumption that the effects of midazolam primarily result from actions on the benzodiazepine receptor site on the $GABA_A$ receptor–ionophore. The increase in sVRP area in the presence of bicuculline alone is not surprising, as there is a marked level of tonic GABA inhibition in the isolated spinal cord, as there is glycine inhibition[27]. The increase observed with flumazenil is surprising. Flumazenil is not known to have inverse agonist effects and is considered to be a pure antagonist at the benzodiazepine site. If this is the case, then the effect of flumazenil itself on the sVRP implies an endogenous ligand at the benzodiazepine receptor.

The synergism observed between midazolam and alfentanil, the ability of naloxone to antagonize the effects of both, and the tendency of midazolam to prevent naloxone-precipitated hyperresponsiveness and the development of opioid tolerance and dependence[12,13] may share a common mechanism, at least in part. We have shown that naloxone-precipitated hyperresponsiveness after μ opioids is blocked by the non-competitive NMDA receptor antagonist MK-801[15,16]. MK-801 also potentiated the effect of morphine[16]. To account for these observations, we have proposed that μ opioids exert a long-lasting underlying excitatory effect that opposes their overwhelming depressant effect, and that is revealed when the depressant effect is abolished by the antagonist. The excitatory effect is proposed to be related to the initial steps in the development of tolerance or dependence. In common with the latter, it appears to be dependent on NMDA receptors[28–36]. It has been proposed that opioids activate protein kinase C, leading to phosphorylation of the NMDA receptor and increased activity through the latter[37].

The effect of benzodiazepines on this system may be to decrease activity through NMDA receptors, thus blocking the excitatory effects of alfentanil and apparently potentiating the opposing depressant effects. The mechanism may involve the relative hyperpolarization that occurs when currents are increased at the $GABA_A$ receptor. Magnesium block of the NMDA receptor is voltage-dependent and enhanced by hyperpolarization. Thus benzodiazepines may block NMDA receptors indirectly and reduce the excitatory effects of alfentanil. In agreement with this hypothesis, propofol, another agent which increases activity at GABA receptors, also potentiates the effect of alfentanil (Feng and

Kendig, unpublished data). Alternative hypotheses are possible, including actions of midazolam on sites other than the GABA_A receptor and a non-linear summation of the effects of enhanced GABA activity mediated via benzodiazepines and membrane hyperpolarization caused by actions of morphine on a second messenger-modulated potassium channel.

The results of this study are relevant to benzodiazepine–opioid analgesia at the spinal level and to benzodiazepine attenuation of the development of opioid tolerance. Opposing benzodiazepine effects at supraspinal levels may complicate the situation in intact animals when benzodiazepines are administered systemically. Benzodiazepines given intrathecally potentiate opioid analgesia, but given intracerebroventricularly inhibit opioid analgesia[38 39]. GABAergic agonists in periaqueductal grey and rostral ventromedial medulla may inhibit descending inhibition of spinal nociceptive neurotransmission. Benzodiazepines, which enhance GABA_A actively, may exert opposing spinal and supraspinal effects on nociceptive neurotransmission. Such opposing effects may contribute to the uncertainty regarding their analgesic properties.

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References

1. Luger TJ, Hayashi T, Lorenz IH, Hill HF. Mechanisms of the influence of midazolam on morphine antinociception at spinal and supraspinal levels in rats. *European Journal of Pharmacology* 1994; **271**: 421–431.
2. Luger TJ, Hayashi T, Weiss CG, Hill HF. The spinal potentiation effect and the supraspinal inhibitory effect of midazolam on opioid-induced analgesia in rats. *European Journal of Pharmacology* 1995; **275**: 153–162.
3. Edwards M, Serrao JM, Gent JP, Goodchild CS, Chir B. On the mechanism by which midazolam causes spinally mediated analgesia. *Anesthesiology* 1990; **73**: 273–277.
4. Yanez A, Sabbe MB, Stevens CW, Yaksh TL. Interaction of midazolam and morphine in the spinal cord of the rat. *Neuropharmaco*logy 1990; **29**: 359–364.
5. Clavier N, Lombard MC, Besson JM. Benzodiazepines and pain: effects of midazolam on the activities of nociceptive non-specific dorsal horn neurones in the rat spinal cord. *Pain* 1992; **48**: 61–71.
6. Dirig DM, Yaksh TL. Intrathecal baclofen and muscimol, but not midazolam, are antinociceptive using the rat-formalin model. *Journal of Pharmacology and Experimental Therapeutics* 1995; **275**: 219–227.
7. Rattan AK, McDonald JS, Tejwani GA. Differential effects of intrathecal midazolam on morphine-induced antinociception in the rat: role of spinal opioid receptors. *Anesthesia and Analgesia* 1991; **73**: 124–131.
8. Rattan AK, Sribanditmongkol P. Effect on morphine-induced catalepsy, lethality, and analgesia by a benzodiazepine receptor agonist midazolam in the rat. *Pharmacology, Biochemistry and Behavior* 1994; **48**: 357–361.
9. Vinik HR, Bradley EL, Kissin I. Triple anesthetic combination: propofol–midazolam–alfentanil. *Anesthesia and Analgesia* 1994; **78**: 354–358.
10. Kissin I, Brown PT, Bradley EL. Sedative and hypnotic midazolam–morphine interactions in rats. *Anesthesia and Analgesia* 1990; **71**: 137–143.
11. Kissin I, Vinik HR, Castillo R, Bradley EL. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesthesia and Analgesia* 1990; **71**: 65–69.
12. Kissin I, Brown PT, Bradley EL jr. Does midazolam inhibit the development of acute tolerance to the analgesic effect of alfentanil? *Life Sciences* 1992; **52**: 55–60.
13. Tejwani GA, Rattan AK, Sribanditmongkol P, Sheu M-J, Zuniga J, McDonald JS. Inhibition of morphine-induced tolerance and dependence by a benzodiazepine receptor agonist midazolam in the rat. *Anesthesia and Analgesia* 1993; **76**: 1052–1060.
14. Feng J, Kendig JJ. Selective effects of alfentanil on nociceptive-related neurotransmission in neonatal rat spinal cord. *British Journal of Anaesthesia* 1995; **74**: 691–696.
15. Feng J, Kendig JJ. *N*-methyl-D-aspartate receptors are implicated in hyperresponsiveness after naloxone reversal of alfentanil in isolated rat spinal cord. *Neuroscience Letters* 1995; **189**: 128–130.
16. Feng JQ, Kendig JJ. The NMDA receptor antagonist MK-801 differtially modulates μ and κ opioid actions in spinal cord *in vitro. Pain* 1995; in press.
17. Lozier AP, Kendig JJ. Long-term potentiation in an isolated peripheral nerve–spinal cord preparation. *Journal of Neurophysiology* 1995; **74**: 1001–1009.
18. Woodley SJ, Kendig JJ. Substance P and NMDA receptors mediate a slow nociceptive ventral root potential in neonatal rat spinal cord. *Brain Research* 1991; **559**: 17–21.
19. Yanagisawa M, Murakoshi T, Tamai S, Otsuka M. Tail-pinch method *in vitro* and the effects of some antinociceptive compounds. *European Journal of Pharmacology* 1985; **106**: 231–239.
20. Thompson SWN, Dray A, Urban L. Injury-induced plasticity of spinal reflex activity: NK1 neurokinin receptor activation and enhanced A- and C-fiber mediated responses in the rat spinal cord *in vitro. Journal of Neuroscience* 1994; **14**: 3672–3687.
21. Kendig JJ, Savola MKT, Woodley SJ, Maze M. Alpha-2 adrenoceptors inhibit a nociceptive response in neonatal rat spinal cord. *European Journal of Pharmacology* 1991; **192**: 293–300.
22. Ishizuki M, Yanagisawa M. Antinociceptive effects of tizanidine, diazepam and eperisone in isolated spinal cord–tail preparations of newborn rat. *Pain* 1992; **48**: 101–106.
23. Tarasiuk A, Grossman Y, Kendig JJ. Barbiturate alteration of respiratory rhythm and drive in isolated brainstem–spinal cord of newborn rat: Studies at normal and hyperbaric pressure. *British Journal of Anaesthesia* 1990; **66**: 88–96.
24. Chou T-C. The median-effect principle and the combination index for quantitation of synergism and antagonism. In: Chou T-C, Rideout DC, eds. *Synergism and Antagonism in Chemotherapy*. San Diego: Academic Press, 1991; 61–102.
25. Boulter N, Serrao JM, Gent JP, Goodchild CS. Spinally mediated antinociception after intrathecal chlorodiazepoxide–further evidence for a benzodiazepine spinal analgesic effect. *European Journal of Anaesthesio*logy 1991; **8**: 407–411.
26. Serrao JM, Goodchild CS, Gent JP. Reversal by naloxone of spinal antinociceptive effects of fentanyl, ketocyclazocine and midazolam. *European Journal of Anaesthesio*logy 1991; **8**: 401–408.
27. Gibbs LM, Kendig JJ. Substance P and NMDA receptor-mediated slow potentials in neonatal rat spinal cord: age-related changes. *Brain Research* 1992; **595**: 236–241.
28. Basbaum AI. Insights into the development of opioid tolerance. *Pain* 1995; **61**: 349–352.
29. Elliott K, Minami N, Kolesnikov YA, Pasternak GW, Inturrisi CE. The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, N^G-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. *Pain* 1994; **56**: 69–75.
30. Tiseo PJ, Cheng J, Pasternak GW, Inturrisi CE. Modulation of morphine tolerance by the competitive *N*-methyl-D-aspartate receptor antagonist LY274614: assessment of opioid receptor changes. *Journal of Pharmacology and Experimental Therapeutics* 1994; **268**: 195–201.
31. Bhargava HN, Matwyshyn GA. Dizocilpine (MK-801) blocks tolerance to the analgesic but not to the hyperthermic effect of morphine in the rat. *Pharmacology* 1993; **47**: 344–350.
32. Kolesnikov YA, Ferkany J, Pasternak GW. Blockade of mu and kappa_1 opioid analgesic tolerance by NPC17742, a novel NMDA antagonist. *Life Sciences* 1993; **53**: 1489–1494.
33. Lutfy K, Hurlbut DE, Weber E. Blockade of morphine-induced analgesia and tolerance in mice by MK-801. *Brain Research* 1993; **616**: 83–88.
34. Tiseo PJ, Inturrisi CE. Attenuation and reversal of morphine tolerance by the competitive N-methyl-D-aspartate receptor antagonist, LY274614. *Journal of Pharmacology and Experimental Therapeutics* 1993; **264**: 1090–1096.
35. Marek P, Ben-Eliyahu S, Gold M, Liebeskind JC. Excitatory amino acid antagonists (kynurenic acid and MK-801) attenu-

ate the development of morphine tolerance in the rat. *Brain Research* 1991; **547**: 77–81.

36. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. *Science* 1991; **251**: 85–87.
37. Mayer DJ, Mao J, Price DD. The development of morphine tolerance and dependence is associated with translocation of protein kinase C. *Pain* 1995; **61**: 365–374.
38. Luger TJ, Hayashi T, Lawrence I, Hill HF. Mechanisms of the influence of midazolam on morphine antinociception at spinal and supraspinal levels in rats. *European Journal of Pharmacology* 1994; **271**: 421–431.
39. Luger TJ, Hayashi T, Weiss CG, Hill HF. The spinal potentiation effect and the supraspinal inhibitory effect of midazolam on opioid-induced analgesia in rats. *European Journal of Pharmacology* 1995; **275**: 153–162.

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Differential effects of ketamine and pentobarbitone on acetylcholine release from the rat hippocampus and striatum

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Summary

Using microdialysis, we examined the effects of ketamine and pentobarbitone on acetylcholine (ACh) release from the rat hippocampus and striatum. Ketamine 25 and 50 mg kg^{-1} increased ACh release from the hippocampus to 295% and 353% of basal release, respectively, but not from the striatum. SCH 23390 1 µmol litre^{-1}, a D1 antagonist, significantly inhibited the facilitatory effect of ketamine 50 mg kg^{-1} on hippocampal ACh release (to 241% of basal level). In contrast, pentobarbitone 20 and 40 µmg kg^{-1} decreased basal ACh release from both the hippocampus by 41% and 69%, respectively, and the striatum by 37% and 58%, respectively. The results suggest that ketamine and pentobarbitone exert opposite effects on ACh release from the rat hippocampus and that the stimulating effect of ketamine may involve dopamine D1 receptors. (*Br. J. Anaesth.* 1996;**77**:381–384)

Key words

Anaesthetics i.v., ketamine. Acetylcholine. Hypnotics barbiturate, pentobarbitone. Brain, hippocampus. Brain, striatum. Rat.

Glutamate receptors coupled to ion channels are classified into two major groups: those that are preferentially stimulated by the agonist *N*-methyl-D-aspartate (NMDA) and those that respond preferentially to other agonists (AMPA/kainate or non-NMDA receptors)[1]. It is generally accepted that ketamine, an i.v. general anaesthetic, is a non-competitive antagonist of NMDA receptors[2–4]. Ketamine has been termed a "dissociative" anaesthetic because patients who receive ketamine alone appear to be in a cataleptic state[5]. The effects of ketamine on the gross electrical activity of the brain show marked differences from that of "depressant" anaesthetics, such as pentobarbitone[1]. Ketamine increases electrical activity in the brainstem reticular formation and limbic structures but the mechanisms are not yet fully understood.

Neurones releasing acetylcholine (ACh) are distributed widely in the brain and may be involved in memory, learning and motor functions[6]. The hippocampus receives abundant extrinsic cholinergic innervation from the medial septal area which contains choline acetyltransferase-positive neurones. The septo–hippocampal cholinergic system is considered to be under the control of dopaminergic neurones. Indeed, several studies suggest that the hippocampus is regulated by dopamine activity, primarily at dopamine-1 (D1) receptors and that D1 agonists increase ACh release in the hippocampus[7 8]. In contrast, the striatum is very important for the control of motor activity, and intrinsic neurones of the striatum are believed to be mostly GABA (gamma-aminobutyric acid)ergic and cholinergic[9 10]. The most important afferent projections appear to be the nigrostriatal dopaminergic pathway and the glutamatergic corticostriatal bundle[9 10]. We hypothesize that the differences in anaesthetic mechanisms between dissociative and depressant anaesthetics may be because of different effects on ACh release in several brain regions.

The aim of this study was to investigate the effects of ketamine and pentobarbitone on hippocampal and striatal cholinergic neurones, and also to examine the relationship between ketamine and D1 receptor mechanisms in the rat hippocampus.

Materials and methods

We used the microdialysis technique in freely moving rats. The study was approved by the Animal Welfare Committee of Yokohama City University School of Medicine. We studied 61 male, adult Sprague–Dawley rats (weighing 250–350 g), anaesthetized with sodium pentobarbitone 40 mg kg^{-1} i.p. and placed in a stereotaxic apparatus (Model SR-6, Narisige Scient Instrument Lab., Japan). The guide cannula (CMA 10, Carnegie Medicine, Sweden) for penetration of a microdialysis probe was implanted stereotaxically into the right hippocampus (coordinates obtained from the bregma with the skull flat: A: −5.6 mm, L: 5.0 mm, V: 3.8 mm from the atlas of Paxinos and Watson[11]) or the right striatum (coordinates from the bregma : A: 1.0 mm, L: 3.0 mm, V: 4 mm) and fixed in place with cranioplastic cement. After allowing at least 2 days for surgical recovery, microdialysis experiments were performed. The probe (CMA 11, Carnegie Medicine, Sweden) (3-mm long dialysis membrane, od 0.24 mm, molecular weight cut-off of 20 000 Da) was inserted into the guide cannula during light anaesthesia with diethyl ether. Microdialysis probes were perfused with Ringer's solution containing eserine sulphate 10

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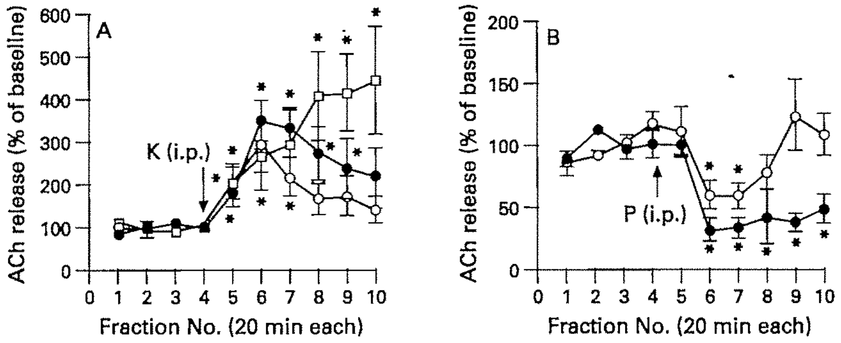

Figure 1 A: Effects of ketamine (K) 25 mg kg^{-1} (○) (n=4), 50 mg kg^{-1} (●) (n=5) and 100 mg kg^{-1} (□) (n=5) i.p. on acetylcholine (ACh) release from the rat hippocampus. B: Effect of pentobarbitone (P) 20 mg kg^{-1} (○) (n=4) and 40 mg kg^{-1} (●) (n=4) i.p. on ACh release from the rat hippocampus. *P<0.05 compared with pre-drug values by ANOVA followed by Student's t test. Data are mean, SEM.

µmol litre^{-1} (Wako Pure Chemical Industries Ltd, Japan), an inhibitor of choline esterase, at 2.0 µl min^{-1}, using a microdialysis pump (Model CMA 102, Carnegie Medicine, Sweden). Implanted probes were pre-perfused with Ringer's solution for 120 min, and then every 20-min perfusate was collected in chilled polyethylene tubes containing 10 µl of ethylhomocholine 1 µmol litre^{-1}, an internal standard for HPLC measurement.

The test drugs used for these experiments were: ketamine 25–100 mg kg^{-1} i.p. (Sankyo Ltd, Japan), pentobarbitone 20–40 mg kg^{-1} i.p. (Abbott Laboratories, USA), MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo [a, d] cyclohepten-5,10-imine hydrogen maleate] 1 mg kg^{-1} i.p. (RBI: Research Biochemicals Incorporated, USA), a non-competitive antagonist of the NMDA receptor and non-anaesthetic agent, and SCH 23390 1 µmol litre^{-1} (local infusion) (RBI: Research Biochemical Incorporated, USA), a D1 antagonist. A new rat was used for each drug dose tested. After four collections, ketamine, pentobarbitone and MK-801 were administered i.p. SCH 23390 was added to the perfusion solution from the start of experiments and continued throughout the experiments.

ACh release was measured by HPLC-ECD using a polymeric reversed-phase column (Eicom-pak AC-GEL, 6.0×150 mm, Eicom, Japan). An AC-Enzympak column (ACh esterase and choline oxidase-immobilized, Eicom, Japan) was used to convert ACh and choline to hydrogen peroxides, which were detected (Model ECD-100, Eicom, Japan) at 450 mV. The mobile phase was phosphate buffer 100 mmol litre^{-1} (pH 8.5), containing tetramethylammonium chloride 65 mg litre^{-1} and decansulphonic acid sodium salt 200 mg litre^{-1}. The limit of sensitivity, defined as a signal-to-noise ratio >5, was 100 fmol (100 fmol/50-µl injection) for ACh and the coefficient of variation (cv) was 2.5% (n=5).

At the end of the experiments, rats were killed by overdose of diethyl ether, and the position of the probe in the brain was confirmed by visual examination. Percentage recovery of the dialysis probes was determined at the end of the experiment by dialysing a beaker containing known concentrations of ACh (here 1 µmol litre^{-1}) at 37 °C. Recovery *in vitro*=C_{out} /C_{in}, where C_{out} =concentration in the perfusate and C_{in}=concentration in the medium. Average ACh recovery through the probes at a flow rate of 2 µl min^{-1} was 16.2 (SEM 1.5) % (n=11). Basal release was obtained from the mean of four initial collections before administration of test drugs and data are expressed as percentage of basal ACh release. The significance of differences between mean values was determined by ANOVA followed by Student's t test.

Results

ACh release was stable for 120 min with baseline ACh concentrations in 20-min samples of 1.1 (SEM 0.2) pmol per sample from the hippocampus (n=39) and 6.7 (0.8) pmol per sample from the striatum (n=22).

Figure 1A and 1B show the effects of ketamine and pentobarbitone on ACh release from the hippocampus. Ketamine 25 and 50 mg kg^{-1} i.p. increased ACh release from the hippocampus in a concentration-dependent manner. The mean maximum increases in ACh release by ketamine 25 and 50 mg kg^{-1} i.p. were 295% and 353% of basal levels, respectively. Peak values of the mean increase were measured in the second sample after i.p. injection of ketamine 25 and 50 mg kg^{-1} (fraction No. 6), and ACh release declined gradually. Ketamine 100 mg kg^{-1} increased ACh release from the rat hippocampus more slowly, but ACh release remained elevated 120 min after i.p. administration (fig. 1A). There were no significant differences between the effects of ketamine 50 and 100 mg kg^{-1} i.p. in the hippocampus.

MK-801 1 mg kg $^{-1}$ i.p. significantly increased ACh release from the rat hippocampus to 338 (22.5)% (n=4) of baseline. In contrast, pentobarbitone 20 and 40 mg kg^{-1} i.p. decreased ACh release from the hippocampus in a concentration-dependent manner. Mean maximum decreases produced by pentobarbitone 20 and 40 mg kg^{-1} i.p. were 41% and 69% of basal levels, respectively (fig. 1B).

In the hippocampus, SCH 23390 1 µmol litre^{-1} (a D1 antagonist) significantly inhibited the facilitatory effect of ketamine 50 mg kg^{-1} i.p. (peak value 241% of basal levels) (n=4), while SCH 23390 1 µmol litre^{-1} alone failed to alter ACh release (fig. 2).

Figure 3A and 3B show the effects of ketamine and pentobarbitone on ACh release from the striatum. Ketamine 25, 50 and 100 mg kg^{-1} i.p. did not affect ACh release, while pentobarbitone 20 and 40 mg kg^{-1} i.p. decreased ACh release by 37% and 58% of basal levels, respectively.

Discussion

"*In vivo*" brain microdialysis techniques, coupled with a highly sensitive analytical method based on

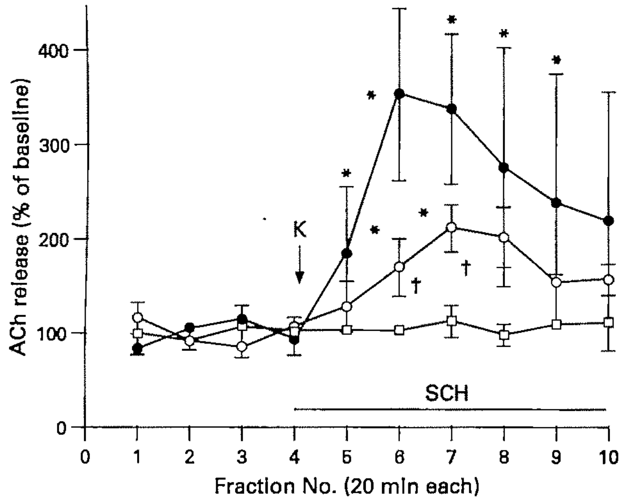

Figure 2 Effect of ketamine (K) 50 mg kg^{-1} i.p. (●) (n=5) and SCH 23390 1 μmol litre^{-1} (SCH) (local infusion), alone (□) (n=7) or in combination (○) (n=6), on ACh release from the rat hippocampus. Ketamine was administered i.p. and SCH was added to the perfusion solution. *P<0.05 compared with pre-drug values by ANOVA followed by Student's t test; †P<0.05 compared with ketamine 50 mg kg^{-1} i.p. by Student's t test. Data are mean, SEM.

HPLC-ECD, have recently made it possible to measure various neurotransmitters in freely moving rats. This permits a precise analysis of the effects of various anaesthetic agents on neurotransmission in the various brain regions[12]. For example, previous studies indicated that diazepam reduced release of dopamine in both the nucleus accumbens and striatum of conscious rats[13], and morphine increased release of serotonin in the rat forebrain[14]. Our study examined the differential effects of ketamine and pentobarbitone on ACh release from the hippocampus and striatum using *in vivo* microdialysis combined with HPLC-ECD.

Pentobarbitone decreased ACh release from the rat hippocampus and striatum, which may suggest a powerful "depressant" anaesthetic effect of pentobarbitone. Previous studies have shown that benzodiazepine agonists decreased ACh release in the hippocampus[15] or striatum[16]. In contrast, ketamine 25–100 mg kg^{-1} i.p. increased ACh release from the rat hippocampus. Our data demonstrated that the facilitatory effect of ketamine 100 mg kg^{-1} was slower and sustained, while that of ketamine 25 or 50 mg kg^{-1} was monophasic, although the underlying mechanisms remain to be determined.

Cocaine and amphetamine have also been shown to increase ACh release from the rat hippocampus[17].

As cocaine and amphetamine are known to increase extraneuronеal concentrations of endogenous dopamine in different dopaminergic areas[17], it appears that, in the hippocampus, ketamine may have a facilitatory role in controlling dopamine release. Furthermore, it might be suggested that these opposite effects of ketamine and pentobarbitone on ACh release from the rat hippocampus underlie the different properties of dissociative and depressant anaesthetics.

ACh release from the rat hippocampus may be linked to cognitive function[17]. Cholinergic projections to the hippocampus originate from the perikarya in the medial septum and vertical limb of the diagonal band of Broca. Cholinergic activity in the hippocampus is increased during arousal, defined by behaviour or electroencephalography[8]. Increased levels of hippocampal ACh accompanied by improved memory were demonstrated. It appears that elevated hippocampal cholinergic function may improve performance of certain cognitive tasks[8]. A report that ketamine prevented the formation of flavour memories supports these findings[2]. Ketamine may have a direct effect on learning or memory storage according to our data and this may be why patients anaesthetized with ketamine experienced bad dreams. Our study does not allow a clear conclusion as to the precise mechanism through which ketamine increases ACh release from the hippocampus. However, SCH 23390, a D1 antagonist, significantly attenuated the effect of ketamine on ACh release in our study, indicating that the facilitatory effect of ketamine might involve D1 receptor mechanisms, at least in part. Day and Fibiger, and Imperato, Obinu and Gessa demonstrated that cholinergic activity in the hippocampus is increased via D1 receptor mechanisms[7,8].

In the striatum, ketamine did not affect ACh release, while pentobarbitone decreased ACh release. We have reported that ACh release from the striatum was increased via D1 receptor mechanisms and decreased via D2/D3 receptor mechanisms[18,19]. It might be suggested that ketamine has an important role in the regulation of ACh release from the rat hippocampal region, but not from the rat striatum, indicating regional selectivity between depressant anaesthetics such as pentobarbitone.

The highest density of NMDA receptors is found in the hippocampus[1]. As MK-801also increased ACh release in the hippocampus, NMDA block seems to underlie the effects of ketamine and is not simply a

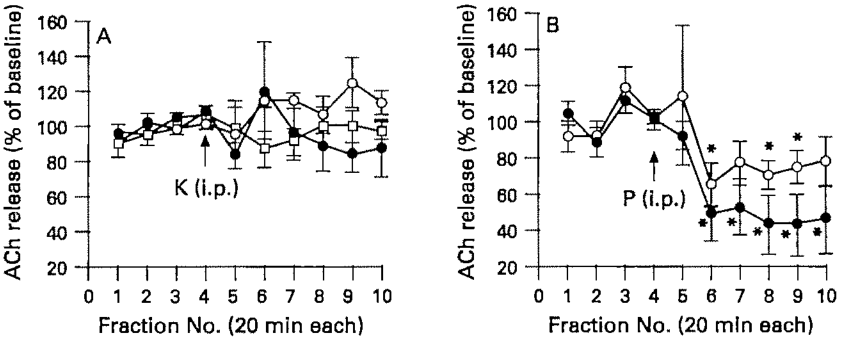

Figure 3 A: Effects of ketamine (K) 25 mg kg^{-1} (○) (n=4), 50 mg kg^{-1} (●) (n=5) and 100 mg kg^{-1} (□) (n=5) (i.p.) on acetylcholine (ACh) release from the rat striatum. B: Effects of pentobarbitone (P) 20 mg kg^{-1} (○) (n=4) and 40 mg kg^{-1} (●) (n=4) i.p. on ACh release from the rat striatum. *P<0.05 compared with pre-drug values by ANOVA followed by Student's t test. Data are mean, SEM.

result of different anaesthetic properties. However, the *in vivo* effects of NMDA receptors on the activity of cholinergic neurones in the hippocampus are still poorly understood. Recent molecular evidence showed that block of NMDA receptors increased the effects of dopamine on D1 receptors[20]. Considering these results, NMDA receptor antagonists, such as ketamine or MK-801, might be expected to increase ACh release from the rat hippocampus via D1 receptor mechanisms. Although our study of the effects of ketamine on ACh release needs further elaboration, it might help to explain the relationship between NMDA and D1 receptors in the rat hippocampus.

In summary, ketamine increased ACh release from the hippocampus, but not from the striatum, while pentobarbitone decreased ACh release from both the hippocampus and striatum. These results may underlie the differences between dissociative and depressant anaesthetics. Further, our data showed that the stimulatory effect of ketamine on ACh release from rat hippocampus may involve dopamine D1 receptors.

References

1. Brockmeyer DM, Kendig JJ. Selective effects of ketamine on amino acid-mediated pathways in neonatal rat spinal cord. *British Journal of Anaesthesia* 1995; **74**: 79–84.
2. Aguado L, Antonio AS, Pérez L, Valle R, Gómez J. Effects of the NMDA receptor antagonist ketamine on flavor memory: conditioned aversion, latent inhibition, and habituation of neophobia. *Behavioral and Neural Biology* 1994; **61**: 271–281.
3. Davies SN, Alford ST, Coan EJ, Lester RAJ, Collingridge GL. Ketamine blocks an NMDA receptor-mediated component of synaptic transmission in rat hippocampus in a voltage-dependent manner. *Neuroscience Letters* 1988; **92**: 213–217.
4. Lalonde R, Joyal CC. Effect of ketamine and L-glutamic acid diethyl ester on concept learning in rats. *Pharmacology, Biochemistry and Behavior* 1991; **39**: 829–833.
5. Reves JG, Glass PSA. Non barbiturate intravenous anesthetics. In: Miller RD, ed. *Anesthesia,* 4th Edn. New York: Churchill Livingstone, 1994; 247–289.
6. Cooper JR. Unsolved problems in the cholinergic nervous system. *Journal of Neurochemistry* 1994; **63**: 395–399.
7. Day JC, Fibiger HC. Dopaminergic regulation of septohippocampal cholinergic neurons. *Journal of Neurochemistry* 1994; **63**: 2086–2092.
8. Imperato A, Obinu MC, Gessa GL. Stimulation of both dopamine D1 and D2 receptors facilitates in vivo acetylcholine release in the hippocampus. *Brain Research* 1993; **618**: 341–345.
9. Sandor NT, Lendvai B, Vizi ES. Effect of selective opiate antagonists on striatal acetylcholine and dopamine release. *Brain Research Bulletin* 1992; **29**: 369–373.
10. Stoof JC, Drukarch B, DeBoer P, Westerink BHC, Groenewegen HJ. Regulation of the activity of striatal cholinergic neurones by dopamine. *Neuroscience* 1992; **47**: 755–770.
11. Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coodinates,* 2nd Edn. New York: Academic Press, 1986.
12. Toide K, Arima T. Effects of cholinergic drugs on extracellular levels of acetylchoine and choline in rat cortex, hippocampus and striatum studied by brain dialysis. *European Journal of Pharmacology* 1989; **173**: 133–141.
13. Invernizzi R, Pozzi L,Samanin R. Release of dopamine is reduced by diazepam more in the nucleus accumbens than in the caudate nucleus of conscious rats. *Neuropharmacology* 1991; **30**: 575–578.
14. Tao R, Auerbach SB. Increased extracellular serotonin in rat brain after systemic or intraraphe administration of morphine. *Journal of Neurochemistry* 1994; **63**: 517–524.
15. Imperato A, Dazzi L, Obinu MC, Gessa GL, Biggio G. Inhibition of hippocampal acetylcholine release by benzodiazepines: antagonism by flumazenil. *European Journal of Pharmacology* 1993; **235**: 135–137.
16. Takada T, Murai T, Kanayama T, Koshikawa N. Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by in vivo microdialysis. *British Journal of Anaesthesia* 1993; **70**: 181–185.
17. Imperato A, Obinu MC, Gessa GL. Effect of cocaine and amphetamine on acetylcholine release in the hippocampus and caudate nucleus. *European Journal of Pharmacology* 1993; **238**: 377–381.
18. Sato K, Ueda H, Okumura F, Misu Y. Supersensitization of intrastriatal dopamine receptors involved in opposite regulation of acetylcholine release in Parkinson's model rats. *Neuroscience Letters* 1994; **173**: 59–62.
19. Sato K, Ueda H, Okumura F, Misu Y. 6-OHDA-induced lesion of the nigrostriatal dopaminergic neurons potentiates the inhibitory effect of 7-OHDPAT, a selective D3 agonist, on acetylcholine release during striatal microdialysis in conscious rats. *Brain Research* 1994; **655**: 233–236.
20. Halpain S, Girault JA, Greengard P. Activation of NMDA receptors induces dephosphorylation of DARPP-32 in rat striatal slices. *Nature (London)* 1990; **343**: 369–372.

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I.v. anaesthetic agents do not interact with the verapamil binding site on L-type voltage-sensitive Ca^{2+} channels

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Summary

In this study we have examined if the i.v. anaesthetic agents thiopentone, pentobarbitone, ketamine, etomidate, propofol and alphaxalone interact with the verapamil binding site on L-type voltage-sensitive Ca^{2+} channels in rat cerebrocortical membranes. Binding assays were performed in 1 ml volumes of Tris HCl 50 mmol litre^{-1}, pH 7.4, for 90 min at 20 °C, with cerebrocortical membranes (200 µg of protein), the verapamil binding sites of which were radiolabelled with [^{3}H]verapamil. Non-specific binding was defined in the presence of verapamil 10^{-6} mol litre^{-1}. The interaction of i.v. anaesthetics was determined by displacement of [^{3}H]verapamil 0.2 nmol litre^{-1}. The mean concentrations of anaesthetic producing 25% inhibition of specific binding (corrected for the competing mass of [^{3}H]verapamil), K_{25}, were (mmol litre^{-1}): thiopentone 0.68 (SEM 0.14); pentobarbitone 1.22 (0.13); propofol 0.66 (0.10); etomidate 0.24 (0.03); alphaxalone 0.19 (0.02); and ketamine 0.75 (0.04). These concentrations exceeded those seen during anaesthesia and suggest that the neuronal verapamil binding site may not be an important target for i.v. anaesthetic agents. (*Br. J. Anaesth.* 1996;**77**:385–386)

Key words

Ions, calcium. Ions, ion channels, kinetics. Model, rat. Anaesthetics i.v.

We have suggested previously that the dihydropyridine (DHP) binding site on neuronal L-type voltage-sensitive Ca^{2+} channels (VSCC) may be a target site for i.v. anaesthetic agents[1]. It is not known if other binding sites on the L-type VSCC, such as verapamil or diltiazem sites, are also involved. However, Maze and colleagues reported that verapamil significantly augmented anaesthetic potency (see Hirota and Lambert[1 2]). As the verapamil binding site resides, together with the DHP binding site, on the α_1 subunit of the channel, we have examined if this site is a target for i.v. anaesthetic agents.

Materials and methods

Female Wistar rats (250–300 g) were stunned and then decapitated. The brain was removed rapidly, the cerebrocortex detached from its internal structures, and homogenized at 4 °C using a tissue Tearor (setting 5,5×30-s bursts) in Tris HCl 50 mmol litre^{-1}, pH 7.4. The homogenate was centrifuged at 18 000 *g* for 10 min and the pellet resuspended in Tris HCl buffer. This procedure was repeated three times. Membranes were frozen in aliquots at −40 °C.

All binding assays were performed in 1 ml volumes of Tris HCl buffer for 90 min at 20 °C using approximately 200 µg of cerebrocortical membrane protein. In order to determine if an i.v. anaesthetic agent interacts with the verapamil binding site on neuronal L-type VSCC, the binding site was labelled with [^{3}H]verapamil ([*N*-methyl-^{3}H]-verapamil hydrochloride, 60.8 Ci mmol^{-1}). Increasing concentrations of i.v. anaesthetic agents as unlabelled displacers were then added. Displacement of [^{3}H]verapamil binding by i.v. anaesthetic agents indicates that they are interacting at the same site as the radiolabel. A fixed concentration of [^{3}H]verapamil (0.2 nmol litre^{-1}) was displaced by the following unlabelled anaesthetics: thiopentone (n=6: 3×10^{-6}–10^{-3} mol litre^{-1}), pentobarbitone (n=6: 3×10^{-6}–10^{-3} mol litre^{-1}), ketamine (n=6: 10^{-4}–10^{-2} mol litre^{-1}), etomidate (n=6: 10^{-6}–3×10^{-4} mol litre^{-1}), propofol (n=6: 3×10^{-6}–10^{-3} mol litre^{-1}) and alphaxalone (n=6: 10^{-6}–3×10^{-4} mol litre^{-1}). Stock solutions were made as follows: thiopentone (100 mmol litre^{-1} stock in NaOH 0.1 mol litre^{-1}), pentobarbitone (50 mmol litre^{-1} stock in distilled water), propofol (100 mmol litre^{-1} stock in DMSO), alphaxalone (50 mmol litre^{-1} stock in DMSO), etomidate (50 mmol litre^{-1} stock in HCl 0.1 mol litre^{-1}) and ketamine (500 mmol litre^{-1} stock in distilled water). Appropriate solvent concentrations were added to control tubes. Non-specific binding was defined in the presence of excess (10^{-6} mol litre^{-1}) verapamil (25 mmol litre^{-1} stock in distilled water).

After incubation, each sample was filtered under vacuum through Whatman GF/B filters using a Brandell cell harvester to separate bound and free radioactivity. Filter retained (bound) radioactivity was extracted for at least 8 h in 4 ml of scintillation fluid and then estimated using a beta scintillation counter. The estimated radioactivity was quench corrected with an average [^{3}H] counting efficiency of 60.4%. The highest anaesthetic concentration used was usually limited by agent solubility.

The concentration of displacer producing 25% and 50% displacement of specific binding (IC_{25} and

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Table 1 Effects of i.v. anaesthetic agents on $[^3H]$verapamil binding (mean (SEM), n=6. *Peak plasma concentration during anaesthesia (see Hirota and Lambert[1])

Agent	K_{25} (mmol litre^{-1})	K_{50} (mmol litre^{-1})	Plasma (μmol litre^{-1})*
Thiopentone	0.68 (0.14)	1.29 (0.19)	83
Pentobarbitone	1.22 (0.13)	4.86 (0.94)	155
Propofol	0.66 (0.10)	1.04 (0.08)	39
Etomidate	0.24 (0.03)	0.49 (0.07)	4.1
Ketamine	0.75 (0.04)	1.52 (0.13)	8.0
Alpaxalone	0.19 (0.02)	0.36 (0.06)	7.5

IC_{50}) was calculated by computer-assisted curve fitting (Graphpad-Prism) and corrected for the competing mass of $[^3H]$verapamil using a K_d of 94 nmol litre^{-1}[3], according to Cheng and Prusoff[4], to yield the affinity constants (K_{25} and K_{50}). All data are expressed as mean (SEM).

Results

All i.v. anaesthetics displaced specific $[^3H]$verapamil binding in a dose-dependent manner. K_{25} and K_{50} values are shown in table 1. These concentrations exceeded those seen during anaesthesia.

Discussion

Two studies[1,2] have suggested that L-type VSCC may be involved in the mechanism of general anaesthesia because L-type VSCC blockers enhanced anaesthetic potency. Previous work from our laboratory[1] indicated that DHP binding sites on neuronal L-type VSCC may be a target site for i.v. anaesthetic agents. We hypothesized that i.v. anaesthetic agents should interact with the verapamil binding site as we have shown previously an interaction with the DHP binding site. Both verapamil and DHP sites reside on the α_1 subunit of the channel, although at different structural motifs[5]. Our data clearly demonstrated that the verapamil binding site is not an important target for i.v. agents as the K_{25} (and K_{50}) exceeded the plasma concentration seen during anaesthesia (see Hirota and Lambert[1,2]). K_{25} values are quoted in addition to K_{50} values, as clinically relevant concentrations of many anaesthetic agents depress Ca^{2+} entry by 20–30%[2]. Collectively, our data suggest that a specific region of the L-channel may act as a target for i.v. agents.

However, verapamil has been reported to decrease the MAC for halothane in dogs and significantly augment the anaesthetic potency of dexmedetomidine or ketamine (see Hirota and Lambert[1,2]). Chikhale, Burton and Borchard[6] suggested that verapamil caused a significant increase in the permeability of the blood–brain barrier, although verapamil itself does not pass the blood–brain barrier. Therefore, this enhancement of anaesthetic potency may not be a direct interaction with the channel (consistent with our data) but may simply enhance agent delivery to the CNS target site(s).

In conclusion, these data indicate that i.v. anaesthetic agents are unable to interact with the verapamil binding site on L-type VSCC at clinically relevant concentrations.

Acknowledgements

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References

1. Hirota K, Lambert DG. I.v. anaesthetic agents inhibit dyhydropyridine binding to L-type voltage-sensitive Ca^{2+} channels in rat cerebrocortical membranes. *British Journal of Anaesthesia* 1996; **77**: 248–253.
2. Hirota K, Lambert DG. Voltage-sensitive Ca^{2+} channels and anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 344–346.
3. Reynolds IJ, Gould RJ, Snyder SH. $[^3H]$Verapamil binding sites in brain and skeletal muscle: regulation by calcium. *European Journal of Pharmacology* 1983; **95**: 319–321.
4. Cheng YC, Prusoff WM. Relationship between the inhibition constant (K_I) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochemical Pharmacology* 1973; **22**: 3099–3108.
5. McDonald TF, Pelzer S, Trautwein W, Pelzer D. Regulation and modulation of calcium channels in cardiac, skeletal, and smooth muscle cells. *Pharmacological Reviews* 1994; **74**: 366–507.
6. Chikhale EG, Burton PS, Borchard RT. The effect of verapamil on the transport of peptides across the blood–brain-barrier in rats—kinetic evidence for an apically polarized efflux mechanism. *Journal of Pharmacology and Experimental Therapeutics* 1995; **273**: 298–303.

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Flow cytometry evaluation of the *in vitro* influence of four i.v. anaesthetics on respiratory burst of neutrophils

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Summary

Exposure of neutrophils to anaesthetic agents may alter their functional characteristics and in patients undergoing long-term sedation this may be clinically relevant. We have investigated the *in vitro* influence of propofol, thiopentone, methohexitone and midazolam on phorbol 12-myristate 13-acetate (PMA)-induced respiratory burst of neutrophils by the intracellular oxidative transformation of dihydrorhodamine-123 to the fluorescent dye rhodamine-123 via flow cytometry. We tested *in vitro* concentrations similar to sedating, anaesthetic, 10-fold sedating and 10-fold anaesthetic plasma concentrations. All drugs showed similar inhibition of respiratory burst at sedating concentrations (1–6%). At anaesthetic concentrations, propofol produced significantly higher mean inhibition (7.3%) compared with thiopentone (4.5%) and methohexitone (0.9%). At 10-fold anaesthetic concentrations inhibition of respiratory burst by propofol was almost complete (90.8%) and significantly higher than that by thiopentone (29.2%) and methohexitone (1.8%). Methohexitone and midazolam had only minimal effects at all concentrations. The effect of the solvent of propofol (10% Intralipid) was similar to that of propofol. Thus suppression of respiratory burst of neutrophils by propofol may be caused by this lipid carrier. (*Br. J. Anaesth.* 1996;**77**:387–392)

Key words

Anaesthetics I.v., propofol. Anaesthetics i.v., thiopentone. Anaesthetics i.v., methohexitone. Hypnotics benzodiazepine, midazolam. Measurement techniques, flow cytometry. Blood, neutrophils.

Blood neutrophils are one of the major cell populations acting against microbial infections. Alteration of neutrophil function by i.v. anaesthetics is currently under intensive laboratory investigation[1]. O'Donnell and colleagues found significant suppression of neutrophil polarization by propofol and thiopentone, which is a change in morphology as a response to a chemotactic stimulus[2]. Another group described a decrease in chemotaxis produced by propofol and its lipid carrier Intralipid after zymosan stimulation[3].

Another important aspect for bacterial killing is neutrophil respiratory burst. The respiratory burst enzyme in the plasma membrane of neutrophils catalyses the oxidation of NADPH which leads to the production of superoxide anion. This production of oxygen radicals is responsible for killing phagocytosed micro-organisms[4–6]. The importance of respiratory burst for defence of bacterial infections is evident in patients with chronic granulomatous disease, which is a congenital disturbance of respiratory burst enzyme activity. These young patients suffer from recurrent severe bacterial infections because their phagocytes are unable to produce superoxide anion, or at best produce only very low levels[7]. Thus it is possible that impairment of neutrophil respiratory burst by i.v. anaesthetics may be hazardous, especially for intensive care patients at risk.

Rothe, Oser and Valet have shown that oxygen radical production during respiratory burst can be quantified in real-time with multiparameter flow cytometry (MFC) using the dye dihydrorhodamine-123 (DHR) which reacts with free radical-derived oxidants to become the brightly green fluorescent rhodamine-123 (rho-123)[8]. MFC simultaneously assesses five variables per measured event: relative cell (particle) size, density (granularity) and three fluorescences, representing surface, intracellular or cell cycle characteristics. Compared with chemiluminescence, which estimates only non-specific oxygen radical generation, the methodology of this study has the advantage of assessing specific intracellular oxygen radical production by plasma membrane respiratory burst oxidase of a certain cell population such as neutrophils.

Thus we have evaluated if propofol, thiopentone, methohexitone or midazolam can modulate phorbol 12-myristate 13-acetate (PMA)-induced respiratory burst of human neutrophils. The concentrations of the drugs tested *in vitro* were adjusted to be similar to plasma concentrations reported for anaesthesia or sedation and also 10-fold higher concentrations[2 9]. As propofol is dissolved in 10% Intralipid for i.v. use and it has been reported that parenteral lipid emulsions can influence the cellular immune response[10–13], we also investigated the effect of 10% Intralipid on respiratory burst.

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Subjects and methods

The study was approved by the Institution Ethics Committee. Informed consent was obtained from the blood donors.

ANAESTHETIC AGENTS

Different concentrations of propofol (Disoprivan, ICI Pharma, Plankstadt, Germany), its lipid carrier, 10% Intralipid (Pharmacia, Erlangen, Germany), thiopentone (Trapanal, Byk Gulden, Konstanz, Germany), methohexitone (Brevimytal Natrium, Eli Lilly, Bad Homburg, Germany) and midazolam (Dormicum, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) on neutrophil respiratory burst were studied. As midazolam is suitable for anaesthesia only in combination with other agents, there are no anaesthetic plasma concentrations defined. Thus midazolam was analysed only at reported sedating doses. Thiopentone and methohexitone were purchased as dry material and dissolved in isotonic saline solution (0.9% NaCl). The desired concentrations of all tested drugs were standardized with phosphate-buffered saline (PBS, Dulbeco's without Ca^{2+} and $MgCl_2$, Gibco BRL, Eggenstein, Germany).

SAMPLE PREPARATION

Heparinized (10 u. ml^{-1}, Liquemin N, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) venous blood samples (3 ml) were obtained from healthy blood donors (n=20). Blood was layered on equal Ficoll quantity (Ficoll-Paque: density 1.077 g dl^{-1}, Biochrom, Berlin, Germany). PBS was portioned (1 ml) and warmed to 37 °C. The nucleated blood cells of the supernatant were harvested after 1 *g* sedimentation at 22 °C for 45 min and resuspended in PBS. Then 30 µl of the leucocyte sample (containing 5×10^5 cells ml^{-1}) and DHR 15 µl (1×10^4 mol, MoBiTec, Goettingen, Germany) were added to the PBS and incubated at 37 °C for 5 min. Subsequently, the cell suspensions were incubated with the drug and concentrations tested at 37 °C for 10 min. Neutrophils from the samples were stimulated with PMA 10 µl (1×10^{-6} mol, Sigma, Deisenhofen, Germany) at 37 °C for 20 min. Stimulation was then terminated by transferring the samples onto ice. Viability discrimination was performed by addition of propidium iodide (PI) 10 µl (3×10^{-3} mol, Serva, Heidelberg, Germany) just before measurement. Internal positive (full PMA stimulation) and negative (no PMA) controls for each sample were carried out without addition of the tested substances. Full stimulation of neutrophil respiratory burst for the positive controls was titrated and considered 1×10^{-6} mol PMA (data not shown).

MULTIPARAMETER FLOW CYTOMETRY

Samples were analysed on a fluorescence-activated cell scanner (FACScan, Becton Dickinson Immunocytometry Systems- BDIS, Heidelberg, Germany). A minimum of 15 000 events per sample were acquired. The flow cytometer was equipped with an argon ion laser, adjusted to an excitation wavelength of 488 nm and 0.5 W. Rho-123 fluorescence emission was filtered and acquired from the corresponding photomultiplier (FL1) in the band spectrum 515–545 nm. The photomultiplier for FL2 and FL3 was used for acquisition of PI emission over the range 563–607 nm. Forward light scatter (FSC), sideward light scatter (SSC) and fluorescence signals were adjusted with the negative and positive control samples. SSC data were collected in linear mode whereas FSC and the fluorescences were collected in logarithmic amplification mode without compensation. A relatively high threshold level of FSC (channels $>10^2$) was set to exclude erythrocytes and cell debris. Data files were stored in list mode using FACScan software and analysed with the PC-Lysis software (BDIS). Two analytical gates were used for precise discrimination of the desired neutrophils (fig. 1A, C and D). Briefly, neutrophils were included by setting an arbitrary leucocyte right-angled gate in FSC *vs* SSC (fig. 1A). Further restriction of neutrophils was performed after zooming leucocytes (R1) in the same dot plot (fig. 1B), as shown elsewhere[14]. Additionally, dead cells were gated and excluded (R2) because of the high fluorescence in FL3 as a result of intracellular PI content (fig. 1C). Thus inhibition of neutrophil respiratory burst was estimated on approximately 5000 remaining events using the negative and positive controls, and an appropriate threshold in SSC *vs* FL1 (fig. 1D).

CALCULATION AND STATISTICS

The percentage of respiratory burst inhibition by the drugs was calculated using the formula:

$$\% \text{ inhibition}=((\text{positive control})-(\text{tested drug})/\text{total viable neutrophils})\times100$$

where positive control=number of rho-123 positive events by full stimulation with PMA; negative control=number of rho-123 positive events without stimulation with PMA and without drug; tested drug=number of rho-123 positive events by stimulation with PMA in the actual drug incubated sample; viable neutrophils=PI negative neutrophils.

As numeric data showed a Gaussian distribution, descriptive statistics, mean (SD), paired two-tailed Student's *t* test for inter-group significance ($P<0.05$, 95% confidence intervals) and Forman's regression were used for statistical analysis of the flow cytometry data (n=20 for each drug and concentration). Otherwise, the non-parametric Mann–Whitney *U* test was used (SPSS/PC V6.01 software package, SPSS, Munich, Germany).

Results

Overall inhibition of neutrophil respiratory burst by propofol, thiopentone, methohexitone and midazolam is illustrated in figures 2 and 3. The percentages of PI positive neutrophils were low for all drugs and concentrations tested (<5%).

SEDATING AND 10-FOLD SEDATING DOSES (FIG. 2)

All drugs showed identical low mean inhibition of respiratory burst at the corresponding sedating concentrations (1% and 6%). At 10-fold sedating doses, propofol 30 µg ml^{-1} produced significantly ($P<0.001$) more inhibition (68.6 (11.2)%) compared with the three other drugs. Thiopentone 200 µg ml^{-1} inhibited

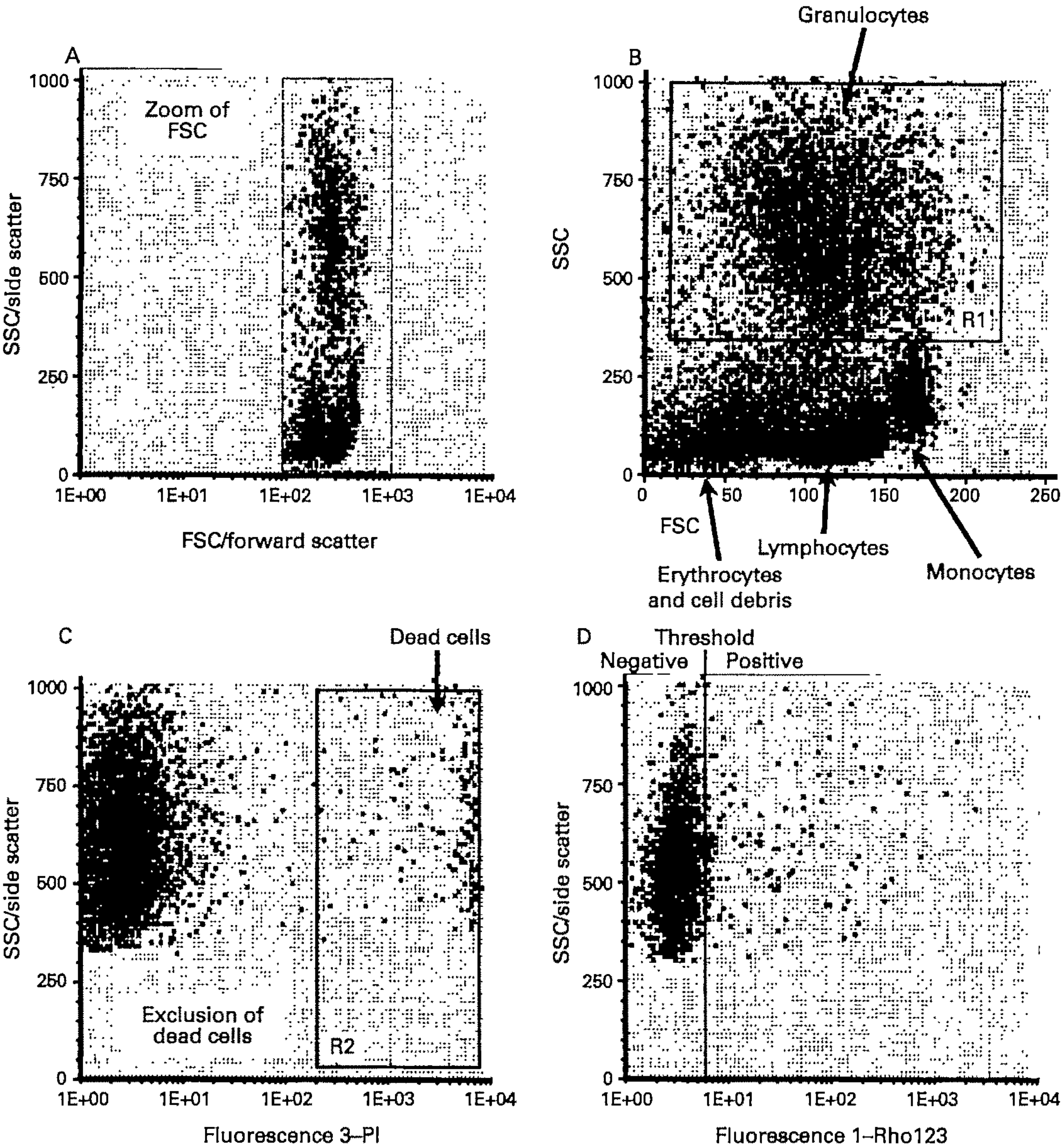

Figure 1 Adjustment of the flow cytometer for acquisition of the desired events (A, C and D) and analysis of neutrophil respiratory burst inhibition (A–D). A: FSC *vs* SSC is depicted as acquired on the flow cytometer. B: Zoomed and localized leucocyte subgroups (R1 granulocytes). C: Exclusion of PI positive cells (R2). D: Threshold setting by overlaying the internal positive and negative control, and by using the gate combination R1 and not R2.

respiratory burst more (14.6 (10.7)%) than methohexitone 50 $\mu g\ ml^{-1}$ (1.3 (1.4)%) and midazolam 6 $\mu g\ ml^{-1}$ (3.4 (3.9)%) at 10-fold sedating concentrations ($P<0.001$). The difference between methohexitone and midazolam was also significant ($P<0.05$).

ANAESTHETIC AND 10-FOLD ANAESTHETIC DOSES (FIG. 3)

At concentrations normally required for anaesthesia, the following significant differences were observed: propofol 6 $\mu g\ ml^{-1}$ and thiopentone 40 $\mu g\ ml^{-1}$ produced greater suppression (7.3 (6.0)% and 4.5 (5.3)%, respectively) ($P<0.001$) than methohexitone 10 $\mu g\ ml^{-1}$ (0.9 (1.6)%). At the highest (10-fold anaesthetic) concentrations, inhibition by propofol 60 $\mu g\ ml^{-1}$ was almost complete (90.8 (3.9)%) and greater ($P<0.001$) than that by thiopentone 400 $\mu g\ ml^{-1}$ (29.2 (15.1)%) and methohexitone 100 $\mu g\ ml^{-1}$ (1.8 (1.7)%), which had only minimal effects.

Significant correlations ($P<0.001$) for the four concentrations with inhibition of respiratory burst were observed with propofol ($r=0.93$) and thiopentone ($r=0.72$). Methohexitone did not inhibit respi-

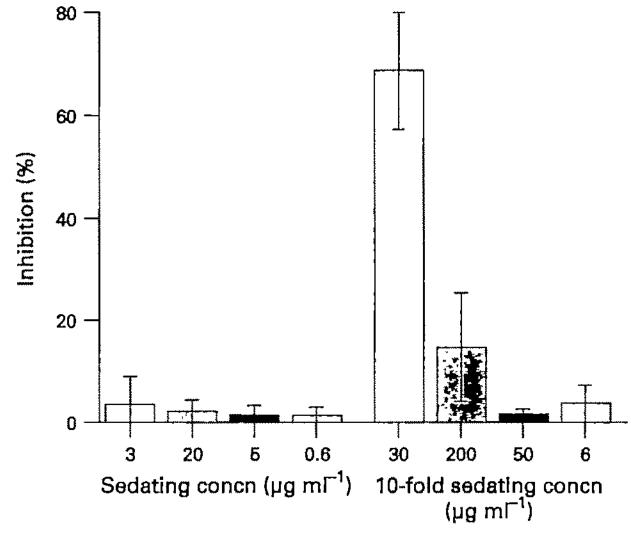

Figure 2 Percentage inhibition of neutrophil respiratory burst produced by propofol (open bars) 3 and 30 $\mu g\ ml^{-1}$, thiopentone (dark shaded bars) 20 and 200 $\mu g\ ml^{-1}$, methohexitone (solid bars) 5 and 50 $\mu g\ ml^{-1}$ and midazolam (light grey bars) 0.6 and 6 $\mu g\ ml^{-1}$ at concentrations likely to be required for sedation and 10-times these concentrations[29].

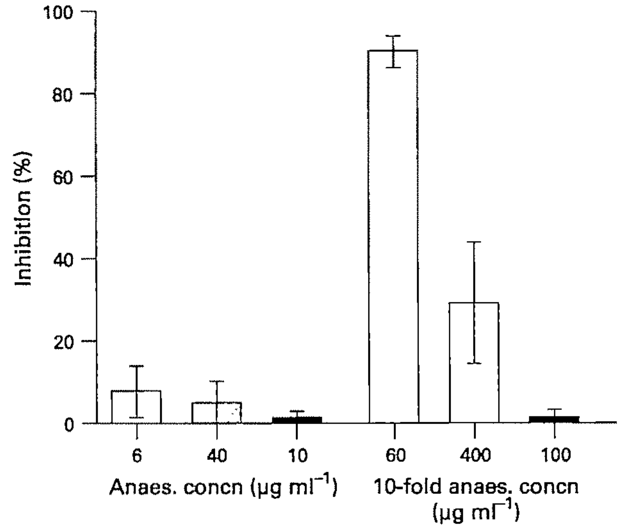

Figure 3 Percentage inhibition of neutrophil respiratory burst produced by propofol (open bars) 6 and 60 µg ml^{-1}, thiopentone (shaded bars) 40 and 400 µg ml^{-1} and methohexitone (solid bars) 10 and 100 µg ml^{-1} at concentrations likely to be required for anaesthesia and 10-times these concentrations[29].

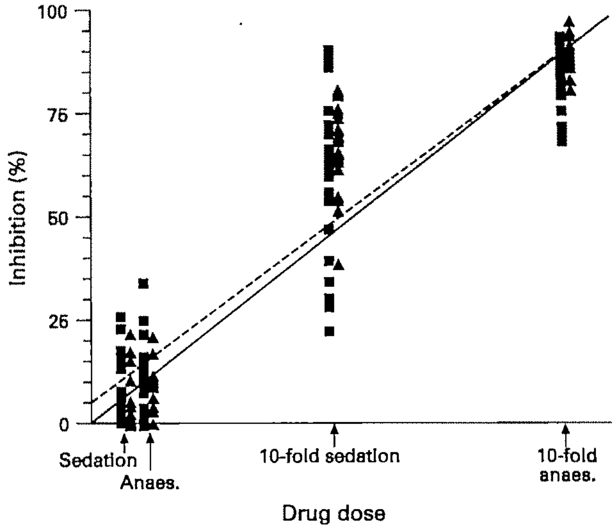

Figure 4 Regression analysis of dose–response relationship of and between propofol (■) (r=0.93, P<0.001) and its lipid carrier vehicle 10% Intralipid (▲) (r=0.9, P<0.001). *In vitro* concentrations of propofol (solid line) likely to be required in plasma during sedation, anaesthesia and 10 times these concentrations (3, 6, 30 and 60 µg ml^{-1}) and the respective volumes of 10% Intralipid (broken line) (0.3, 0.6, 3 and 6 µl ml^{-1})[29].

ratory burst in a dose-related manner. The four volumes of 10% Intralipid (0.3, 0.6, 3 and 6 µl ml^{-1}), which were carrying corresponding concentrations of propofol 3, 6, 30 and 60 µg ml^{-1}, inhibited respiratory burst to the same extent and with significant correlations between the dose inhibition relations of propofol (r=0.93) and 10% Intralipid (r=0.90). There were no significant differences between the effects of both drugs (fig. 4).

Only in samples incubated with the highest concentration (10-fold anaesthetic) of propofol (60 µg ml^{-1}, 452(75)) and with the equivalent volume of 10% Intralipid (6 µl ml^{-1}, 443(80)) was there a significant decrease in mean side scatter signal intensity compared with the negative control (mean channel numbers 550 (SD 143)) (fig. 5).

Discussion

METHODOLOGY

We have studied the *in vitro* effects of thiopentone, methohexitone, midazolam and propofol on respiratory burst of neutrophils from healthy blood donors after PMA stimulation via multiparameter flow cytometry (MFC). The discrepancy between the published data on the influence of different drugs on *in vitro* neutrophil function is probably because of the variety of techniques used and the sensitivity and fragility of neutrophils. The applied MFC technique has different advantages compared with other methodologies measuring non-specific oxygen radical production, such as chemiluminescence. With the present MFC technique it is possible to measure the direct effects on the responsible enzyme complex, the intracellular respiratory burst oxidase. Moreover, only the intracellular oxygen radical content of one selected cell population is investigated and several variables of each cell are evaluated at the same time. In this study, five variables of 15 000 cells for each sample were assessed and four variables of approximately 5000 viable neutrophils were analysed. Thus the high number of analysed events resulted in data with low coefficients of variation. The objectivity of the procedure was maintained by repeated device adjustment and the use of external and internal positive and negative controls. Cell toxicity as a possible explanation for the effects of the drugs studied was excluded by staining with fluorochrome propidium iodide (PI). PI can only attach to cellular DNA after destruction or disintegration of cell membranes, usually subsequent to cell death[14]. Only PI-negative cells (i.e. viable cells) were included in the estimation.

THIOPENTONE

The thiobarbiturate thiopentone produced dose-related suppression of respiratory burst. The highest mean suppression of up to 30% was reached with 10-fold the concentrations found in plasma during anaesthesia. The oxybarbiturate methohexitone had only minimal effects at all concentrations studied, without any dose–effect correlation. A former study showed that thiopentone suppressed *N*-formylmethionyl-leucyl-phenylalanine (FMLP)-induced neutrophil chemiluminescence and chemotaxis, even at plasma concentrations in the therapeutic range[15]. Suppression of neutrophil migration and chemiluminescence by thiobarbiturates was 10–100 stronger than that by oxybarbiturates and was attributed to the sulphur atom in the thiobarbiturate molecule[16]. Additionally, lymphocyte functions such as mitogen-induced blast transformation and cell proliferation appeared to be markedly more impaired in the presence of thiopentone than other barbiturates[17]. Eberhardt and colleagues reported an increase in pulmonary infections of up to 40% in patients with brain oedema undergoing mechanical ventilation and receiving thiopentone. Higher doses of thiopentone were associated with development of infections[18]. The reported observations and our observed suppression of intracellular oxygen radical production by thiopentone may favour the use of oxybarbiturates in

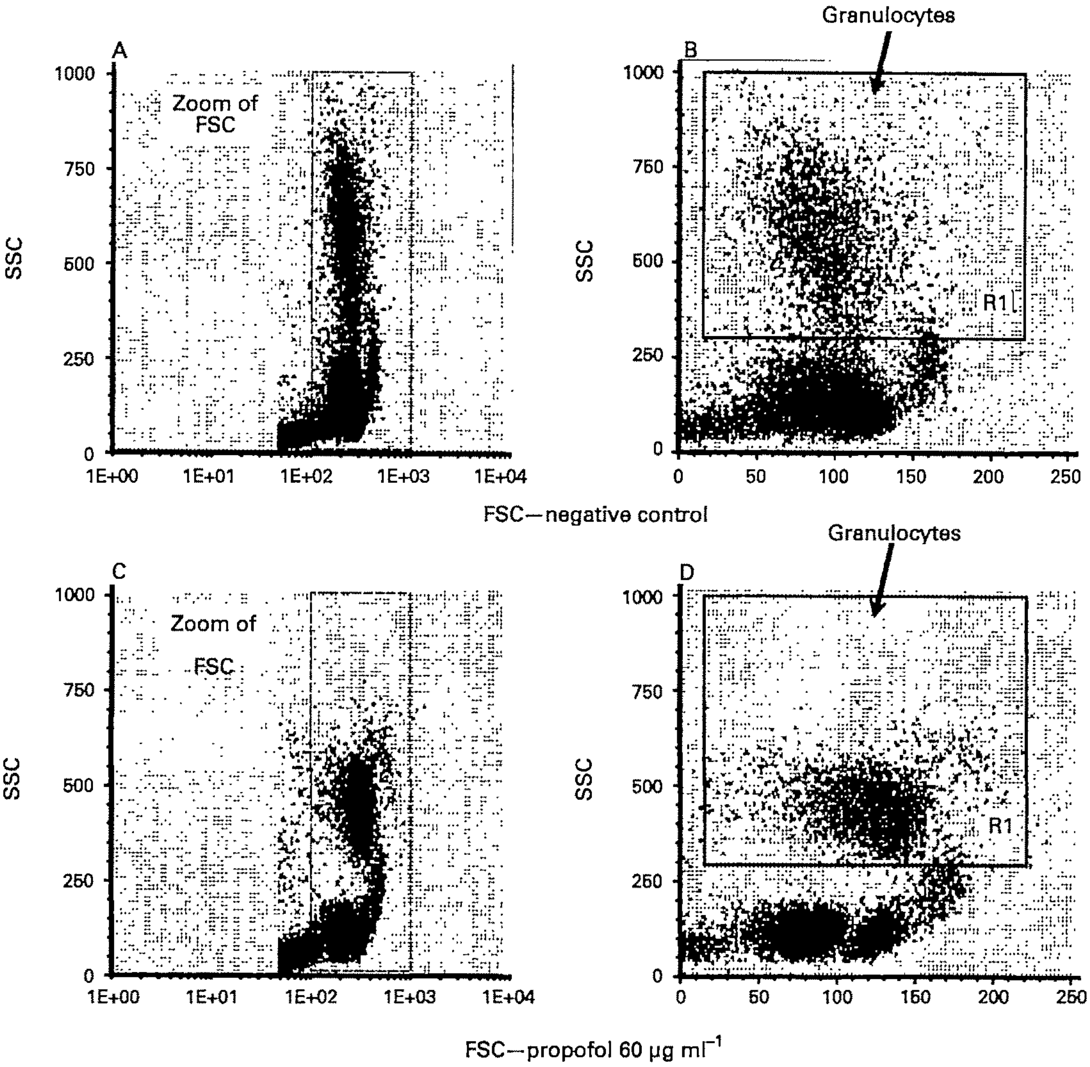

Figure 5 Decrease in SSC signals of neutrophils incubated with 10-fold anaesthetic doses of propofol (60 μg ml^{-1}) compared with the negative control. A (negative control) and C (propofol 60 μg ml^{-1}) are depicted as acquired on the flow cytometer. Changing FSC from logarithmic to linear scale and gating the neutrophils (R1) leads to figures B (negative control) and D (propofol 60 μg ml^{-1}). The SSC signals were decreased from B to C. As estimated in a SSC histogram over the gated neutrophils (R1), peak, mean (SD) and median channel numbers were as follows: 456, 452 (75) and 450 for propofol, and 553, 550 (143) and 550 for the negative control, respectively.

induced barbiturate coma during brain oedema than thiobarbiturates.

MIDAZOLAM

The influence of midazolam on respiratory burst after PMA stimulation was negligibly low. Finnerty and colleagues described stimulus-dependent inhibition of superoxide anion production by benzodiazepines measured by chemiluminescence. Benzodiazepines specifically repressed FMLP- but not PMA-stimulated neutrophil superoxide anion production[19]. Stimulation by FMLP is receptor-mediated by a formyl peptide receptor on the surface of the neutrophil granulocytes, whereas PMA activates respiratory burst oxidase through its ability to stimulate protein kinase C[6]. Suppression of neutrophil respiratory burst oxidase by benzodiazepines was found to be mediated by a specific peripheral receptor[20]. Thus stimulation with FMLP may not correlate with PMA stimulation. However, the clinical relevance of this phenomenon remains unclear.

PROPOFOL

Propofol produced the greatest inhibition of respiratory burst with tested concentrations. At 10-fold anaesthetic concentrations, suppression was almost complete (90.8%). It is not clear if the effects of propofol on leucocyte function are induced by its lipid carrier, 10% Intralipid. In a previous study, propofol was found to suppress whereas 10% Intralipid augmented neutrophil polarization[2], which is in contrast with another study, where propofol and 10% Intralipid suppressed neutrophil chemotaxis[3].

INTRALIPID

We found that propofol and equal volumes of 10% Intralipid inhibited respiratory burst to the same extent and with a significant dose–response correlation. Thus the effects of propofol on respiratory burst may be attributed to its lipid carrier. Moreover, it is well known that parenteral lipid emulsions suppress some aspects of leucocyte function. Numerous authors have described impairment of antimicrobial defence[9 10 21], chemotaxis[21 22] and T cell-mediated immunity[11 12 23]. Additionally, accumulation of particles was described in the cytoplasm of neutrophils, which correlated with reduced cell function after parenteral i.v. lipid infusions[24]. This observation correlates with the fact that polyunsaturated fatty acids can be incorporated rapidly into cell membranes[25] and increase membrane rigidity[26].

Intralipid 10% is composed of high concentrations of long chain triglycerides (LCT) containing unsaturated fatty acids. The increase in membrane rigidity in the presence of LCT may result in the observed reduction in chemotactic properties. These changes in membrane structure may also provide an explanation for the decrease in SSC signals of neutrophils found in this study, because SSC characterizes cell granularity, density or membrane folding. This decline was observed only with the highest concentrations of propofol (10-fold anaesthetic dose, 60 μg ml^{-1}) and the corresponding volume of 10% Intralipid (6 μl ml^{-1}) alone. Cell death and a coating phenomenon were excluded, because both fluorescences (FL 1 and 3) were not influenced. Many studies and the results of our study suggest that parenteral lipid emulsions can inhibit some leucocyte functions.

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References

1. Stevenson GW, Hall SC, Rudnick S, Seleny FL, Stevenson HC. The effect of anesthetic agents on the human immune response. *Anesthesiology* 1990; 72: 542–552.
2. O'Donnell NG, McSharry CP, Wilkinson PC, Asbury A. Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin. *British Journal of Anaesthesia* 1992; **69**: 70–74.
3. Jensen AG, Dahlgren C, Eintrei C. Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*. *British Journal of Anaesthesia* 1993; **70**: 99–100.
4. Babior BM. Oxygen-dependent microbial killing by phagocytes. *New England Journal of Medicine* 1978; **298**: 721–725.
5. Fantone JC, Ward PA. Role of oxygen-derived free radicals and metabolites in leukocyte-dependent inflammatory reactions. *American Journal of Pathology* 1982; 107: 395–418.
6. Babior BM. The respiratory burst oxidase. *Advantages in Enzymology* 1992; **65**: 49–95.
7. Forrest CB, Forehand JR, Axtell RA, Roberts RL, Johnston RB jr. Clinical features and current management of chronic granulomatous disease. In: Curnutte JT, ed. *Hematology/ Oncology. Clinics of North America*. Philadelphia: WB Saunders, 1988; 253–266.
8. Rothe G, Oser A, Valet G. Dihydrorhodamine 123: a new flow cytometric indicator for respiratory burst activity in neutrophil granulocytes. *Naturwissenschaften* 1988; **75**: 354–355.
9. Devlin EG, Clarke RSJ, Mirakhur K, McNeill TA. Effect of four i.v. induction agents on T-lymphocyte proliferations to PHA *in vitro*. *British Journal of Anaesthesia* 1994; **73**: 315–317.
10. Fisher GW, Hunter KW, Wilson SR, Mease AD. Diminished bacterial defences with Intralipid. *Lancet* 1980; **2**: 819–820.
11. Monson JRT, Ramsden CW, MacFie J, Brennan TG, Guillou PJ. Immunorestorative effect of lipid emulsions during total parenteral nutrition. *British Journal of Surgery* 1986; **73**: 843–846.
12. Sedman PC, Ramsden CW, Brennan TG, Guillou PJ. Pharmacological concentrations of lipid emulsions inhibit interleukin-2-dependent lymphocyte responses in vitro. *Journal of Parenteral and Enteral Nutrition* 1990; **14**: 12–17.
13. Sedman PC, Somers SS, Ramsden CW, Brennan TG, Guillou PJ. Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. *British Journal of Surgery* 1991; **78**: 1396–1399.
14. Arseniev L, Goudeva L, Kadar JG, Suedmeier I, Battmer K, Matheja S, Mitschulat H, Stangel W, Link H. Flow cytometry quantification of CD34+ cells and other leucocyte subpopulations in frozen–thawed blood cell suspensions: investigation of a new Teflon container for cryopreservation of haematopoietic progenitor cells. *Infusionstherapie, Transfusionsmedizin* 1995; **22**: 152–158.
15. Weiss M, Buhl R, Birkhahn A, Mirow N, Schneider M, Wernet P. Do barbiturates and their solutions suppress FMLP-induced neutrophil chemiluminescence? *European Journal of Anaesthesiology* 1994; 11: 371–379.
16. Kress HG, Eberlein T, Hoernber B, Weis KH. Suppression of neutrophil migration and chemiluminescence is due to the sulphur atom in the thiobarbiturate molecule. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 122–128.
17. Neuwelt EA, Kikuchi K, Hill SA, Lipsky P, Frenkel E. Barbiturate inhibition of lymphocyte function. Differing effects of various barbiturates used to induce coma. *Journal of Neurosurgery* 1982; **56**: 254–259.
18. Eberhardt KEW, Thimm BM, Spring A, Maskos WR. Dose-dependent rate of nosocomial pulmonary infection in mechanically ventilated patients with brain oedema receiving barbiturates: a prospective case study. *Infection* 1992; **20**: 12–18.
19. Finnerty M, Marczynski TJ, Amirault HJ, Urbancic M, Andersen BR. Benzodiazepines inhibit neutrophil chemotaxis and superoxide production in a stimulus dependent manner; PK11195 antagonizes these effects. *International Journal of Immunopharmacology* 1991; **22**: 185–193.
20. Zavala F, Masson A, Brys L, de Baetselier P, Descamps-Latscha B. A monoclonal antibody against peripheral benzodiazepine receptor activates the human neutrophil NADPHoxidase. *Biochemical and Biophysical Research Communications* 1991; 176: 1577–1583.
21. Fraser I, Neoptolemos J, Woods J. The effect of Intralipid and heparin on human monocyte and lymphocyte function. *Journal of Parenteral and Enteral Nutrition* 1984; **8**: 381–384.
22. Nordenstroem J, Jarstrand C, Wiernik A. Decreased chemotactic and random migration of leukocytes during Intralipid infusion. *American Journal of Clinical Nutrition* 1979; **32**: 2416–2422.
23. Ring J, Seifert J, Mertin J, Brendel W. Prolongation of skin allografts in rats by treatment with linoleic acid. *Lancet* 1974; **2**: 1331.
24. Jarstrand C, Berghem L, Lahnborg G. Human granulocyte and reticuloendothelial system function during Intralipid infusion. *Journal of Parenteral and Enteral Nutrition* 1978; **2**: 663–670.
25. Curtis AS, Shaw FM, Spires VM. Cell surface lipids and adhesion. II. The turnover of lipid components of the plasmalemma in relation to cell adhesion. *Journal of Cell Science* 1975; **18**: 357–373.
26. Mandel G, Clark W. Functional properties of EL-4 tumor cells with lipid-altered membranes. *Journal of Immunology* 1978; **120**: 1637–1643.

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Atrioventricular conduction during adenosine-induced hypotension in dogs anaesthetized with sevoflurane

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Summary

We have studied the effects of adenosine-induced hypotension on A-H interval (atrioventricular (AV) nodal conduction time during sinus rhythm), St-H interval (intra-atrial plus AV nodal conduction time during atrial pacing), H-V interval (His–Purkinje conduction time) and H-S interval (total ventricular conduction time) by His-bundle electrocardiography in addition to surface electrocardiogram during both sinus rhythm and atrial pacing in nine dogs anaesthetized with 1 MAC of sevoflurane. Stepwise increases in infusion rates of adenosine to 0.1, 0.3, 0.5 and 1.0 mg kg^{-1} min^{-1} produced a dose-related decrease in mean arterial pressure from 91 (6) to 38 (2) mm Hg. Adenosine significantly increased the A-H interval at infusion rates of 0.5 mg kg^{-1} min^{-1} and above, and the St-H interval at 1.0 mg kg^{-1} min^{-1}. The H-V and H-S intervals remained unchanged. Heart rate decreased significantly only at 1.0 mg kg^{-1} min^{-1} with a significant increase in the PR interval. Adenosine-induced hypotension did not have deleterious effects on AV conduction times and the surface electrocardiogram in dogs anaesthetized with 1 MAC of sevoflurane. This may indicate that the effects of adenosine on AV conduction were small and therefore are unlikely to be a contraindication to the use of adenosine for inducing hypotension in patients with initially normal conduction during sevoflurane anaesthesia. (*Br. J. Anaesth.* 1996;**77**:393–398)

Key words

Anaesthetics volatile, sevoflurane. Anaesthetic techniques, hypotensive. Heart, conduction. Monitoring, electrocardiography. Pharmacology, adenosine. Dog.

Adenosine has been used as a hypotensive agent during major surgery[1–5]. Unlike other hypotensive agents such as sodium nitroprusside and trinitroglycerin, adenosine is a naturally occurring purine nucleoside and produces rapid and stable hypotension without evidence of biochemical or haematological toxicity[1]. Tachyphylaxis and rebound hypertension have not been reported after induced hypotension with adenosine[1–5]. In addition, adenosine has an extremely short half-life (10–30 s) because of rapid uptake into cells, resulting in rapid termination of action when administration is discontinued[6].

Although adenosine has been shown to cause depression of sinus node automaticity[7 8] and atrioventricular (AV) nodal conduction *in vitro*[9], it is known to be highly effective clinically in terminating re-entrant tachycardia involving the AV node[10]. However, there has been no study on the electrophysiological effects of adenosine on the cardiac conduction system in the presence of inhalation anaesthetics.

Sevoflurane provides rapid control of arterial pressure as a result of its low blood solubility[11 12] and it has no adverse cardiac electrophysiological effects[13]. Therefore, a combination of sevoflurane and adenosine may be used to safely induce hypotension.

We have studied atrioventricular conduction and the surface electrocardiogram during adenosine-induced hypotension in dogs anaesthetized with sevoflurane.

Materials and methods

ANIMAL PREPARATION

The study was approved by the management committee of the Jichi Medical Laboratory of Experimental Medicine, based on the school's 1993 Guide for Laboratory Animals.

Anaesthesia was induced in nine mongrel dogs, weighing 13–21 kg (mean 16.6 kg), by insufflating 3–5% (1.3–2.1 MAC) sevoflurane via a funnel-shaped plastic mask fitted to the dog's face connected to a Jackson–Rees circuit. The trachea was intubated and ventilation was adjusted to maintain normocapnia with a Harvard pump respirator (R-60, Aika, Co., Ltd).

Anaesthesia for surgical preparation was maintained with 2–3% end-tidal concentrations of sevoflurane and 50% nitrous oxide in oxygen delivered into the inspiratory limb of a Harvard pump respirator. Sevoflurane was vaporized using a Sevotec vaporizer (Penlon Inst., Ltd). A micromanometer-tipped catheter (7F 45326, Toyoda Instr., Ltd) was inserted via the left femoral artery into the abdominal aorta to measure systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures.

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A catheter was inserted into the abdominal aorta via the right femoral artery to sample arterial blood for measurement of pH, Pa_{O_2}, Pa_{CO_2} and serum electrolyte concentrations. Lactated Ringer's solution was infused at a rate of 5–10 ml kg^{-1} h^{-1} via the left femoral vein throughout the study. Body temperature was measured with an oesophageal thermistor and maintained at 36–37 °C using an external heating blanket.

A right thoracotomy was performed at the fifth intercostal space. A quadripolar electrode catheter introduced via the right femoral vein was positioned under manual control across the tricuspid valve to obtain a stable His-bundle electrogram (HBE). The His-bundle catheter electrodes were connected to a switch box that allowed selection of any combination of two electrodes. The output of the switch box was connected to a preamplifier with bandwidth cutoff frequencies of 40–1000 Hz. The electrodes of the surface electrocardiogram (ECG: lead II and V5) were connected to another preamplifier with a filter bandwidth of 0.1–120 Hz. The output from each preamplifier was recorded on a thermal recorder (8M15, NEC San-ei, Ltd, Tokyo, Japan) at a paper speed of 100 mm s^{-1}. Heart rate was determined by counting QRS complexes over 10 s. Arterial pressures and surface ECG were recorded on a multichannel recorder (Recti-Horiz-8K, NEC San-ei, Ltd, Tokyo, Japan).

HBE was recorded at a paper speed of 500 mm s^{-1} to calculate AV conduction intervals with 1.0-ms resolution (Visigraph 5L37, NEC San-ei, Ltd, Tokyo, Japan). An electrode for atrial pacing was attached to the surface of the right atrial appendage. An R-wave coupled cardiac stimulator (3F61, NEC San-ei, Instr., Ltd) delivering rectangular monophasic pulses of 1 ms duration was used for all atrial pacing.

ELECTROCARDIOGRAPHIC AND ELECTROPHYSIOLOGICAL MEASUREMENTS

RR, PR and St-R intervals, QRS duration and QT interval were measured from ECG lead II. The PR interval during sinus rhythm was measured from the onset of the P wave to the onset of the Q wave of the QRS complex. The St-R interval during atrial pacing was measured from the beginning of the stimulus artefact (St) in the HBE to the onset of the Q wave of the QRS complex. The QT interval was corrected for heart rate by dividing the QT interval by the square root of the RR interval (s) to obtain the QTc interval[14].

AV conduction times measured were as follows: A-H interval (AV nodal conduction time during sinus rhythm); St-H interval (intra-atrial plus AV nodal conduction time during atrial pacing); H-V interval (His–Purkinje conduction time); and H-S interval (total ventricular conduction time). The A-H interval was measured from the beginning of atrial deflection to the beginning of the His-bundle spike in the HBE[15]. The St-H interval was measured from the beginning of the St to the beginning of the His-bundle spike in the HBE[16]. The H-V interval was measured from the beginning of the His-bundle spike to the beginning of the ventricular deflection in the HBE[15]. The H-S interval was measured from the beginning of the His-bundle spike to the end of the rapid ventricular deflection in the HBE[16] (fig. 1).

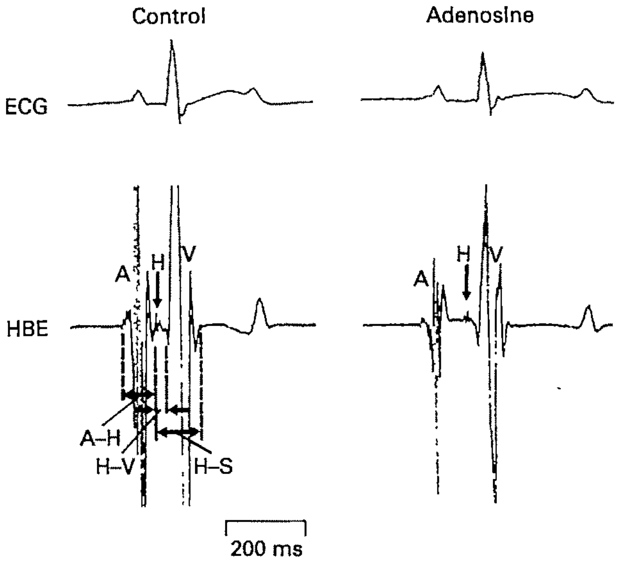

Figure 1 Surface electrocardiogram (ECG, lead II) and His-bundle electrogram (HBE) during sinus rhythm. The A-H and PR intervals were prolonged significantly with an infusion of adenosine 1.0 mg kg^{-1} min^{-1} compared with control. A=Atrial deflection; H=His-bundle spike; V=ventricular deflection; A-H (atrioventricular nodal conduction time)=interval from the beginning of atrial deflection to the beginning of the His-bundle spike in the HBE; H-V (His-Purkinje conduction time)=interval from the beginning of the His-bundle spike to the beginning of the ventricular deflection in the HBE; H-S (total ventricular conduction time)= interval from the beginning of the His-bundle spike to the end of the rapid ventricular deflection in the HBE.

EXPERIMENTAL PROCEDURE

At the end of the surgical procedure, nitrous oxide was discontinued and the end-tidal concentration of sevoflurane was adjusted to 2.4% (1 MAC) and maintained for at least 20 min. After haemodynamic stabilization, control values of the variables noted above were obtained during both sinus rhythm and subsequent atrial pacing. The right atrium was constantly paced at 100 (8) beat min^{-1}, which was slightly faster than the control sinus rate during each infusion of adenosine. Twenty beats were recorded during sinus rhythm, and then the right atrium was paced for 1 min and 20 consecutive beats were recorded. Sinus rhythm returned immediately after pacing was discontinued.

Crystal adenosine (Sigma Chemical Co., St Louis, MO, USA) was dissolved in normal saline at a concentration of 2 mg ml^{-1} and infused into the inferior vena cava. The infusion rate of adenosine was increased stepwise to 0.1, 0.3, 0.5 and 1.0 mg kg^{-1} min^{-1} every 3 min. All measurements and blood sampling were performed 2–3 min after each rate of adenosine was infused during both sinus rhythm and subsequent atrial pacing. Heart rate and arterial pressures were also measured for 5 min after discontinuation of the adenosine infusion.

DATA ANALYSIS

Data are given as mean (SEM). Statistical analysis was performed using analysis of variance (ANOVA) with repeated measures, followed by Scheffe's *F* test. $P<0.05$ was considered statistically significant.

Table 1 Effects of adenosine on arterial pressures and heart rate during sinus rhythm (mean (SEM)). SAP = Systolic arterial pressure; DAP = Diastolic arterial pressure; MAP = Mean arterial pressure. HR = Heart rate *$P < 0.05$ compared with control value; †$P < 0.05$ compared with preceding value

		Infusion rate of adenosine (mg kg^{-1} min^{-1})				
	Control	0.1	0.3	0.5	1.0	5 min after infusion
SAP (mm Hg)	119 (7)	90 (8)*	68 (6)*†	63 (5)*	57 (3)*	126 (4)†
DAP (mm Hg)	76 (6)	47 (5)*	33 (3)*†	31 (2)*	29 (2)*	85 (4)†
MAP (mm Hg)	91 (6)	62 (6)*	45 (4)*†	42 (3)*	38 (2)*	98 (4)†
HR (beat min^{-1})	90 (7)	89 (6)	82 (5)	79 (5)	73 (5)*	89 (8)†

Results

HAEMODYNAMIC EFFECTS (TABLE 1)

Adenosine produced dose-related stable decreases in SAP, DAP and MAP. MAP decreased significantly from 91(6) to 62 (6), 45 (4), 42 (3) and 38 (2) mm Hg with adenosine infusion rates of 0.1, 0.3, 0.5 and 1.0 mg kg^{-1} min^{-1}, respectively. Heart rate remained unchanged at 0.1 mg kg^{-1} min^{-1} and tended to decrease at 0.3 and 0.5 mg kg^{-1} min^{-1}, and decreased significantly at 1.0 mg kg^{-1} min^{-1}. There were no significant differences in SAP, DAP and MAP between control values and those at 5 min after termination of adenosine infusion: rebound hypertension did not occur.

ELECTROPHYSIOLOGICAL AND ELECTROCARDIOGRAPHIC EFFECTS (TABLES 2, 3)

Adenosine significantly increased the A-H interval at infusion rates of 0.5 mg kg^{-1} min^{-1} and above, during sinus rhythm, and the St-H interval only at 1.0 mg kg^{-1} min^{-1} during atrial pacing. There were significant differences between the A-H and St-H intervals under control conditions and at each infusion rate. The H-V and H-S intervals were unchanged during both sinus rhythm and atrial pacing at all infusion rates.

The RR interval was unchanged at an infusion rate of 0.1 mg kg^{-1} min^{-1}, tended to decrease at 0.3 and 0.5 mg kg^{-1} min^{-1} and decreased significantly at 1.0 mg

Table 2 Effects of adenosine on atrioventricular conduction times during sinus rhythm and atrial pacing (mean (SEM)). A-H interval =Atrioventricular (AV) nodal conduction time, H-V interval =His-Purkinje conduction time, H-S interval =total ventricular conduction time, St-H interval = intra-atrial plus AV nodal conduction time during atrial pacing. *$P < 0.05$ compared with control value, ††$P < 0.01$ compared with corresponding value obtained during sinus rhythm

		Infusion rate of adenosine (mg kg^{-1} min^{-1})			
	Control	0.1	0.3	0.5	1.0
Sinus rhythm					
A-H interval (ms)	82.9 (6.7)	84.0 (7.5)	89.1 (8.0)	94.2 (7.6)*	100.4 (7.0)*
H-V interval (ms)	33.1 (3.1)	33.6 (2.9)	32.2 (2.7)	33.8 (3.1)	32.7 (3.5)
H-S interval (ms)	109.4 (5.2)	109.3 (5.3)	108.8 (5.7)	108.7 (5.9)	108.7 (6.0)
Atrial pacing					
St-H interval (ms)	129.6 (12.1)††	124.0 (10.7)††	132.0 (10.8)††	138.7 (10.6)††	147.1 (9.8)*††
H-V interval (ms)	33.6 (3.2)	33.6 (3.2)	32.9 (3.2)	32.9 (3.5)	32.7 (3.5)
H-S interval (ms)	108.6 (5.2)	109.1 (5.3)	108.4 (6.0)	108.7 (6.1)	107.8 (6.3)

Table 3 Effects of adenosine on the surface electrocardiogram during sinus rhythm and atrial pacing (mean (SEM)). QTc interval = QT interval/$\sqrt{RR}$ (s) and St-R interval = interval from stimulus artefact to the onset of the QRS complex. *$P < 0.05$ compared with control value; †$P < 0.05$ compared with corresponding value obtained during sinus rhythm

		Infusion rate of adenosine (mg kg^{-1} min^{-1})			
	Control	0.1	0.3	0.5	1.0
Sinus rhythm					
RR interval (ms)	723.7 (47.7)	696.4 (42.4)	750.1 (37.6)	783.2 (43.8)	849.9 (51.7)*
PR interval (ms)	127.4 (8.4)	127.2 (9.0)	129.9 (9.3)	133.9 (9.3)	139.7 (9.0)*
QRS duration (ms)	62.8 (2.2)	61.8 (2.2)	62.0 (1.9)	63.2 (2.1)	63.9 (2.3)
QT interval (ms)	367.1 (23.1)	362.5 (22.0)	367.7 (19.4)	380.5 (20.5)	390.2 (24.0)
QTc interval (ms)	430.9 (16.7)	433.2 (15.4)	424.0 (14.4)	429.8 (14.3)	423.3 (18.0)
Atrial pacing					
RR interval (ms)	629.6 (47.4)	629.6 (47.4)	629.6 (47.4)†	629.6 (47.4)†	629.6 (47.4)†
St-R interval (ms)	159.6 (14.3)†	153.4 (12.3)†	161.1 (11.7)†	167.7 (12.3)†	176.0 (12.1)*†
QRS duration (ms)	62.8 (2.1)	62.7 (2.5)	62.7 (2.1)	62.6 (1.9)	62.4 (2.4)
QT interval (ms)	351.8 (21.4)	350.6 (23.2)	353.4 (21.9)	357.4 (22.9)	365.6 (24.9)
QTc interval (ms)	443.3 (13.5)	441.1 (15.2)	445.0 (13.2)	449.8 (14.0)	459.4 (15.4)†

kg^{-1} min^{-1}. Pacing rate was 100 (8) beat min^{-1}, which was slightly greater than the control rate at sinus rhythm (90 (7) beat min^{-1}). Adenosine significantly increased the PR interval during sinus rhythm and the St-R interval during atrial pacing, but only at an infusion rate of 1.0 mg kg^{-1} min^{-1}. However, a PR interval longer than 200 ms and AV conduction block did not appear at any infusion rate. The QT interval tended to increase during sinus rhythm, while it was unchanged during atrial pacing. QRS duration and the QTc interval were unchanged during both sinus rhythm and subsequent atrial pacing.

Discussion

We have found that infusion of adenosine produced rapid and dose-related decreases in systolic, diastolic and mean arterial pressures and significantly increased the A-H interval at infusion rates of 0.5 mg kg^{-1} min^{-1} and above during sinus rhythm, and the St-H interval at 1.0 mg kg^{-1} min^{-1} during atrial pacing under anaesthesia with 1 MAC of sevoflurane.

Decreased arterial pressures became stable within 1–1.5 min after the beginning of the infusion of adenosine at each rate. Adenosine-induced hypotension can be attributed to systemic arterial vasodilatation, as shown previously in dogs[17], pigs[18] and humans[1–3]. Rebound hypertension did not occur. This finding is in agreement with a previous report[17].

The haemodynamic and electrophysiological effects of adenosine are influenced by a complex interplay of A_1 and A_2 receptors located on the surface of cell membranes and coupled to G proteins[19]. A_2 receptors in endothelial and vascular smooth muscle cells mediate vasodilatation in almost all vascular beds, including the coronary artery, whereas A_1 receptors in cardiomyocytes mediate two types of actions: one is cyclic AMP (cAMP)-independent (direct actions), shortens the action potential in atrial cells[20], elicits sinus slowing and hyperpolarization of SA nodal cells[8 21] and causes depression of the action potential in AV nodal cells[9]; the other is cAMP-dependent (indirect actions) and antagonizes positive chronotropic, dromotropic and inotropic effects through antagonism of the increase in activity of adenylate cyclase and accumulation of cAMP caused by ß agonists and forskolin[22 23].

In general, adenosine-induced hypotension produces reflex tachycardia via activation of baroreflexes, as is the case with other hypotensive agents, in conscious dogs[24], conscious humans[25] and patients anaesthetized with phenoperidine–droperidol[1]. In this study, adenosine-induced hypotension during 1 MAC of sevoflurane anaesthesia was not accompanied by an increase in heart rate. In fact, heart rate tended to decrease with an increases in the infusion rate of adenosine and decreased significantly at an infusion rate of 1.0 mg kg^{-1} min^{-1}. This finding is in agreement with previous results in pigs anaesthetized with methomidate[17], in dogs anaesthetized with phenoperidine–droperidol[26], in rabbits anaesthetized with halothane[27] and in dogs anaesthetized with halothane–nitrous oxide[4]. These results may be attributed to a direct inhibitory effect of adenosine on the sinus node cells[7] and an indirect inhibitory effect of adenosine on cardiac sympathetic neurotransmission[28]. Our results also suggest that the direct and indirect effects of adenosine on the sinus node during sevoflurane anaesthesia may predominate over activation of baroreflexes induced by hypotension with adenosine.

Inhalation anaesthetics have been shown to depress baroreflex function; the extent of depression varies between anaesthetics, with both halothane[29 30] and enflurane[31] being more depressant than isoflurane[32]. Recently, sevoflurane has been shown to depress baroreflex function in chronically instrumented dogs[33]. In addition, we found in our earlier study that sevoflurane suppressed tachycardia associated with nicardipine-induced hypotension in dogs[34]. Therefore, the direct and indirect inhibitory effects of adenosine could be enhanced by sevoflurane anaesthesia.

Prolongation of the A-H interval with adenosine 0.5 and 1.0 mg kg^{-1} min^{-1} can be attributed to direct depression of the action potential in AV nodal cells[9]. This negative dromotropic effect of adenosine may be responsible for the significant prolongation of the PR interval at 1.0 mg kg^{-1} min^{-1} compared with the control value. Because the sensitivity of the AV node to adenosine in the dog is known to be less than that in human[35], the responses to approximately 5–10 times the clinical dose[2 3] were examined in this study. Heart block did not develop at any infusion rate of adenosine in this study, even in the presence of profound hypotension.

In this study, the right atrium was paced at a slightly higher rate than the original sinus rhythm to exclude the influence of heart rate on AV conduction times. Although the St-H interval increased significantly at 1.0 mg kg^{-1} min^{-1}, no significant differences were observed in the degree of increases between the A-H and St-H intervals at any infusion rate of adenosine. Although it is not clear why the St-H interval was 40–50 ms longer than the A-H interval during sinus rhythm, the differences between the A-H and St-H intervals probably reflected latency between the stimulus and atrial activation. Because incremental increases in atrial-paced rate were not performed, the effects of adenosine on the rate-dependence of AV nodal conduction times during sevoflurane anaesthesia is unclear.

Adenosine did not affect the H-V interval, indicating that the site of the dromotropic action of adenosine is proximal to the His bundle, that is the AV node[9]. Our results are consistent with this finding, because both the H-V and H-S intervals were unchanged during both sinus rhythm and subsequent atrial pacing. The lack of effect of adenosine on QRS duration and the QTc interval during both sinus rhythm and subsequent atrial pacing might reflect the absence of effects of adenosine on the His–Purkinje ventricular conduction system and on the average action potential duration of ventricular muscle, respectively.

Electrophysiological studies with inhalation anaesthetics demonstrated that halothane and enflurane were more depressant of A-V nodal conduction time than isoflurane[36–38]. However, the electrophysiological effects of sevoflurane have not been studied fully. We compared the effects of 1 and 2 MAC of sevoflurane, isoflurane and halothane on specialized AV conduction times in dogs anaesthetized with pentobarbitone[13] where we found that both sevoflurane and isoflurane did not affect the A-H, H-V and H-S intervals, whereas halothane significantly prolonged only the A-H interval at 2 MAC during sinus rhythm, although pentobarbitone might modify the effects of subsequently administered inhalation anaesthetics.

A battery of electrophysiological tests, including measurements of sinus node recovery time, AV nodal refractory periods and Wenckebach cycle length should be performed to provide sufficient information for measurement of the possible clinical electrophysiological risk of adenosine. Non-invasive methods using more adenosine-sensitive animals and higher concentrations of sevoflurane may also be highly desirable. Although there are several limitations, as mentioned above, our results suggest that adenosine should not exert adverse effects on AV conduction times in combination with sevoflurane anaesthesia.

In summary, adenosine-induced hypotension did not elicit reflex tachycardia and adenosine did not produce detrimental heart block during anaesthesia with 1 MAC of sevoflurane. Adenosine may therefore be used as a hypotensive agent during sevoflurane. However, the potential for coronary steal[21, 39] and renal vasoconstriction[22, 40] during adenosine administration may limit its clinical usefulness.

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References

1. Sollevi A, Lagerkranser M, Irestedt L, Gordon E, Lindquist C. Controlled hypotension with adenosine in cerebral aneurysm surgery. *Anesthesiology* 1984; **61**: 400–405.
2. Öwall A, Gordon E, Lagerkranser M, Lindquist C, Rudehill A, Sollevi A. Clinical experience with adenosine for controlled hypotension during cerebral aneurysm surgery. *Anesthesia and Analgesia* 1987; **66**: 229–234.
3. Öwall A, Järnberg P, Brodin L, Sollevi A. Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism in fentanyl anesthetized patients with peripheral vascular disease. *Anestheriology* 1988; **68**: 416–421.
4. Gröndal S, Bindslev L, Sollevi A, Hamberger B. Adenosine: A new antihypertensive agent during pheochromocytoma removal. *World Journal of Surgery* 1988; **12**: 581–585.
5. Öwall A, Sollevi A. Myocardial effects of adenosine- and sodium nitroprusside-induced hypotension: A comparative study in patients anaesthetized for abdominal aortic aneurysm surgery. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 216–220.
6. Möser GH, Schrader J, Deussen A. Turnover of adenosine in plasma of human and dog blood. *American Journal of Physiology* 1989; **256**: C799–C806.
7. West GA, Belardinelli L. Sinus slowing and pacemaker shift caused by adenosine in rabbit SA node. *Pflügers Archiv. European Journal of Physiology* 1985; **403**: 66–74.
8. Belardinelli L, Giles WR, West A. Ionic mechanisms of adenosine actions in pacemaker cells from rabbit heart. *Journal of Physiology (London)* 1988; **405**: 615–633.
9. Clemo HF, Belardinelli L. Effect of adenosine on atrioventricular conduction. I: Site and characterization of adenosine action in the guinea pig atrioventricular node. *Circulation Research* 1986; **59**: 427–436.
10. DiMarco JP, Sellers TD, Berne RM, West GA, Belardinelli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. *Circulation* 1983; **68**: 1254–1263.
11. Kazama T, Ikeda K. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. *Anesthesiology* 1988; **68**: 435–437.
12. Eger EI II, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. *Anesthesia and Analgesia* 1987; **66**: 977–982.
13. Nakaigawa Y, Akazawa S, Shimizu R, Ishii R, Yamato R. Comparison of the effects of halothane, isoflurane, and sevoflurane on atrioventricular conduction times in pentobarbital-anesthetized dogs. *Anesthesia and Analgesia* 1995; **81**: 249–253.
14. Bazett HC. An analysis of the time relations of electrocardiograms. *Heart* 1920; **7**: 353.
15. Fogoros RN. *Electrophysiologic Testing*. Boston: Blackwell Scientific Publications, 1991; 37–61.
16. Atlee JL III, Rusy BF. Atrioventricular conduction times and atrioventricular nodal conductivity during enflurane anesthesia in dogs. *Anesthesiology* 1977; **47**: 498–503.
17. Newberg LA, Milde JH, Michenfelder JD. Cerebral and systemic effects of hypotension induced by adenosine or ATP in dogs. *Anesthesiology* 1985; **62**: 429–436.
18. Norlén K. Central and regional haemodynamics during controlled hypotension produced by adenosine, sodium nitroprusside and nitroglycerin. *British Journal of Anaesthesia* 1988; **61**: 186–193.
19. Lerman BB, Belardinelli L. Cardiac electrophysiology of adenosine: Basic and clinical concepts. *Circulation* 1991; **83**: 1499–1509.
20. Belardinelli L, Isenberg G. Isolated atrial myocytes: Adenosine and acetylcholine increase potassium conductance. *American Journal of Physiology* 1983; **244**: H734–H737.
21. West GA, Belardinelli L. Correlation of sinus slowing and hyperpolarization caused by adenosine in sinus node. *Pflügers Archiv. European Journal of Physiology* 1985; **403**: 75–81.
22. Dobson JG jr. Reduction by adenosine of the isoproterenol-induced increase in cyclic adenosine 3',5'-monophosphate formation and glycogen phosphorylase activity in rat heart muscle. *Circulation Research* 1978; **43**: 785–792.
23. West GA, Isenberg G, Belardinelli L. Antagonism of forskolin effects by adenosine in isolated hearts and ventricular myocytes. *American Journal of Physiology* 1986; **250**: H769–H777.
24. Hintze TH, Belloni FL, Harrison JE, Shapiro GC. Apparent reduction in baroreflex sensitivity to adenosine in conscious dogs. *American Journal of Physiology* 1985; **249**: H554–H559.
25. Conradson TBG, Dixon CMS, Clarke B, Barnes PJ. Cardiovascular effects of infused adenosine in man: potentiation by dipyridamole. *Acta Physiologica Scandinavica* 1987; **129**: 387–391.
26. Lagerkranser M, Irestedt L, Sollevi A, Andreen M. Central and splanchnic hemodynamics in the dog during controlled hypotension with adenosine. *Anesthesiology* 1984; **60**: 547–552.
27. Fukunaga AF, Flacke WE, Bloor BC. Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. *Anesthesia and Analgesia* 1982; **61**: 273–278.
28. Hedqvist P, Fredholm BB. Inhibitory effect of adenosine on adrenergic neuroeffector transmission in the rabbit heart. *Acta Physiologica Scandinavica* 1979; **105**: 120–122.
29. Seagard JL, Hopp FA, Bosnjak ZJ, Elegbe EO, Kampine JP. Extent and mechanism of halothane sensitization of the carotid sinus baroreceptors. *Anesthesiology* 1983; **58**: 432–437.
30. Duke PC, Fownes D, Wade JG. Halothane depresses baroreflex control of heart rate in human. *Anesthesiology* 1977; **46**: 184–187.
31. Morton M, Duke PC, Ong B. Baroreflex control of heart rate in man awake and during enflurane and enflurane–nitrous oxide anesthesia. *Anesthesiology* 1980; **52**: 221–223.
32. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. *Anesthesiology* 1984; **60**: 173–179.
33. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG. Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. *Anesthesiology* 1990; 72: 659–662.
34. Akazawa S, Shimizu R, Kasuda H, Nemoto K, Yoshizawa Y, Inoue S. Effects of sevoflurane on cardiovascular dynamics, coronary circulation and myocardial metabolism in dogs. *Journal of Anesthesia* 1988; **2**: 227–241.
35. Froldi G, Belardinelli L. Species-dependent effects of adenosine on heart rate and atrioventricular nodal conduction. *Circulation Research* 1990; **67**: 960–978.
36. Atlee JL III, Brownlee SW, Burstrom RE. Conscious-state

comparisons of the effects of inhalation anesthetics on specialized atrioventricular conduction times in dogs. *Anesthesiology* 1986; **64**: 703–710.

37. Ozaki S, Gotoh Y, Nakaya H, Azuma M, Kanno M. Electrophysiologic effects of enflurane and halothane on isolated rabbit hearts in the presence and absence of metabolic acidosis. *Anesthesia and Analgesia* 1985; **64**: 1060–1064.
38. Scheffer GJ, Jonges R, Holley HS, Grimbergen CA, Ros HH, Peper A, Booij LHDJ. Effects of halothane on the conduction system of the heart in humans. *Anesthesia and Analgesia* 1989; **69**: 721–726.
39. Hartman JC, Kampine JP, Schmeling WT, Warltier DC. Steal-prone coronary circulation in chronically instrumented dogs: Isoflurane versus adenosine. *Anesthesiology* 1991; **74**: 744–756.
40. Spielman WS, Thompson CI. A proposed role for adenosine in the regulation of renal hemodynamics and renin release. *American Journal of Physiology* 1982; **242**: F423–F435.

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Effects of fentanyl, nitrous oxide, or both, on baroreceptor reflex regulation in the cat

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Summary

We have investigated the effects of fentanyl, nitrous oxide, or both, on carotid sinus baroreceptor reflexes in cats during basal chloralose anaesthesia. The bilaterally isolated carotid sinuses were perfused at prevailing systemic arterial pressure or at predetermined levels of pump-controlled pulsatile pressures of 50–200 mm Hg in steps of 25 mm Hg. Other major baroreceptor sites were denervated by bilateral vagotomy. Fentanyl decreased arterial pressure dose-dependently when the carotid sinuses were perfused at prevailing systemic arterial pressure and when the perfusion pressure was controlled artificially. High-dose fentanyl reduced significantly baroreceptor reflex responses in the sinus perfusion pressure range 50–125 mm Hg. Nitrous oxide increased arterial pressure in the carotid sinus perfusion range 75–125 mm Hg. There was no interaction between nitrous oxide and fentanyl for baroreceptor reflex responses. Our results indicated that baroreceptor reflexes, with and without nitrous oxide, were well preserved by moderate doses of fentanyl while high doses of fentanyl depressed baroreceptor reflexes. (*Br. J. Anaesth.* 1996;77:399–403)

Key words

Reflexes, baroreceptor. Model, cat. Cat. Analgesics opioid, fentanyl. Anaesthetics gases, nitrous oxide.

The baroreflex is very important for short-term cardiovascular homeostasis. Halogenated inhaled anaesthetics decrease arterial pressure in a dose-dependent manner by interaction with both central and peripheral mechanisms. There is evidence also that halogenated inhaled anaesthetics depress the baroreceptor reflex[1]. In contrast, balanced anaesthesia with nitrous oxide and fentanyl is characterized by more stable peroperative haemodynamic conditions. One reason for this might be that this type of anaesthesia blunts baroreceptor reflexes to a lesser degree.

The aim of this study was to investigate the effects of nitrous oxide alone or in combination with fentanyl on the carotid sinus baroreceptor reflex. The study was performed in an experimental model in cats allowing analysis of the carotid sinus open loop gain, that is the impact on systemic arterial pressure of changes in perfusion pressure to the bilaterally isolated carotid sinuses.

Materials and methods

The study was performed on eight cats, weighing 3.2–4.9 kg. The animals had been deprived of food for 12 h but had free access to water. The study was approved by the National Swedish Animal Experiment Ethics Committee.

Anaesthesia was induced with enflurane and 70% nitrous oxide in oxygen and continued with chloralose 50 mg kg^{-1} i.v. as basal anaesthesia. Supplementary doses of chloralose 50 mg were given when necessary during the experiment. After tracheotomy, the lungs were ventilated with air at a frequency of 20 bpm with a Harvard 661 small animal ventilator. Tidal volume was adjusted to maintain an arterial $P\mathrm{co}_2$ of 3.5–4.5 kPa, as verified by repeated arterial blood-gas analyses (ABL-2, Radiometer, Copenhagen).

Hydration and avoidance of metabolic acidosis was accomplished by a continuous infusion (10 ml kg^{-1} h^{-1} during preparation and 5 ml kg^{-1} h^{-1} during experiment) of Ringer's–glucose with the addition of 20 ml of sodium bicarbonate 0.6 mol litre^{-1} per 100 ml. Core temperature was maintained at 37–38 °C by means of a heating pad.

Cardiopulmonary and aortic baroreceptors were denervated by bilateral sectioning of the vagal nerves. The carotid sinuses were bilaterally partly isolated by ligation of the external and sometimes also the internal carotid arteries, and all other arterial branches that could be ligated without endangering the integrity of the sinus nerves by dissection. After administration of heparin 5000 IE i.v., catheters were inserted bilaterally into the common carotid arteries and femoral arteries, allowing the carotid sinuses to be perfused with blood from the femoral arteries, either at systemic arterial pressure by a direct bypass or at any desired level of pulsatile pressure using a rotor pump. To allow adjustments of carotid sinus perfusion pressure without changes in pump frequency, an arteriovenous shunt was inserted between the carotid sinuses and an external jugular vein. The carotid sinus perfusion pressure was recorded from a side branch of the tubing system. This preparation has been described in detail previously[2].

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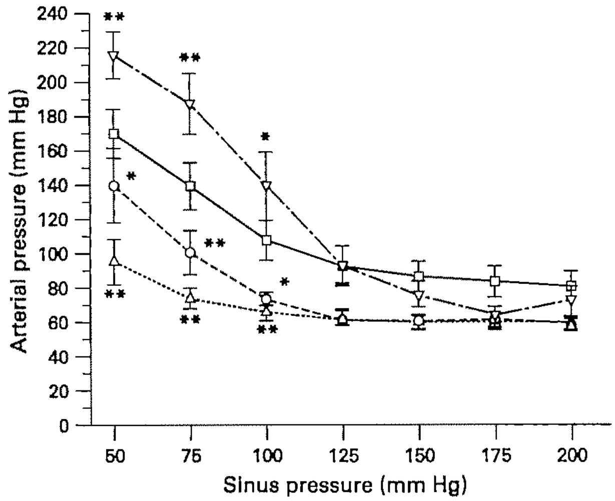

Figure 1 Baroreflex responses (systemic mean arterial pressure (MAP) *vs* carotid sinus perfusion pressure) in animals receiving air (mean, SEM). The following stages are shown: baseline (□); low-dose fentanyl (○); high-dose fentanyl (△); after naloxone (▽). $^{*}P<0.05$, $^{**}P<0.01$ compared with baseline.

The reactivity of the sinus preparation was assessed at the end of the instrumentation by recording how changes in sinus perfusion pressure influenced systemic arterial pressure. The mean maximum open loop gain[3] was 2.2 (SEM 0.3), that is systemic arterial pressure was changed inversely by 2.2 mm Hg per 1 mm Hg change in sinus perfusion pressure, calculated over a pressure interval of 25 mm Hg.

Systolic (SAP) and diastolic (DAP) arterial pressures were measured via a catheter inserted into a brachial artery and recorded on a Grass Polygraph (Grass Instruments, USA). Mean (MAP) arterial pressure was calculated using the formula: MAP=(SAP+2xDAP)/3. Heart rate (HR) was derived electronically from the arterial pressure recording.

Baroreflex activity was evaluated by changing carotid sinus perfusion pressure with arterial inflow to the bypass closed. This was accomplished by setting the pump in the bypass circuit at a steady state rate while a variable portion of the bypass flow was directed through the shunt to the external jugular vein by continuously adjusting a clamp around the shunt tubings. Sinus perfusion pressure was increased by the pump from 50 to 200 mm Hg in steps of 25 mm Hg. Recordings of arterial pressures and HR were performed at steady state after 15 min at each of the following eight stages: (1) ventilation with air; (2) ventilation with 70% nitrous oxide in oxygen; (3) ventilation with air; (4) ventilation with air. Bolus injection of fentanyl 10 μg kg^{-1} followed by an infusion of fentanyl 4 μg kg^{-1} h^{-1}; (5) ventilation with 70% nitrous oxide in oxygen. Continued infusion of fentanyl 4 μg kg^{-1} h^{-1}; (6) ventilation with air. Bolus injection of fentanyl 40 μg kg^{-1} followed by an infusion of fentanyl 16 μg kg^{-1} h^{-1}; (7) ventilation with 70% nitrous oxide in oxygen. Continued infusion of fentanyl 16 μg kg^{-1} h^{-1}; and (8) ventilation with air. At steady state, 15 min after (7), naloxone 30 μg kg^{-1} was injected i.v.

STATISTICAL ANALYSIS

Data were analysed by repeated analysis of variance and Duncan's multiple range test. $P<0.05$ was considered significant. All data are presented as mean (SEM).

Results

CAROTID SINUSES PERFUSED AT SYSTEMIC ARTERIAL PRESSURE

Fentanyl decreased arterial pressure in a dose-dependent manner during air ventilation. Although no significant changes in HR from baseline were induced by fentanyl, HR was significantly lower after the high dose than after the low dose of the drug ($P<0.01$, table 1).

Fentanyl-induced changes in DAP and HR were reversed by naloxone, while SAP and MAP were increased above baseline values ($P<0.01$ and $P<0.05$, respectively, table 1).

Administration of nitrous oxide in oxygen compared with ventilation with air did not induce any significant changes in arterial pressures or HR during basal chloralose anaesthesia with or without the addition of fentanyl (table 2).

CAROTID SINUS PERFUSION PRESSURES CONTROLLED ARTIFICIALLY

Fentanyl decreased MAP throughout the range of carotid sinus perfusion pressures (50–200 mm Hg; ANOVA main effects $P<0.001$ for both fentanyl doses). At sinus perfusion pressures of 50, 75 and 100 mm Hg, fentanyl caused a dose-related decrease in MAP (fig. 1). Baroreflex gain was not changed by low-dose fentanyl, while high-dose fentanyl reduced the gain for sinus perfusion pressure intervals of 50–75, 75–100 and 100–125 mm Hg (fig. 1). Although no significant changes in HR from baseline were induced by fentanyl, HR was significantly lower after high-dose compared with low-dose fentanyl (ANOVA main effects; $P<0.05$, table 3).

Fentanyl-induced decreases in MAP and baroreflex gain were reversed by naloxone. At carotid sinus pressures of 50, 75 and 100 mm Hg, MAP was increased significantly above baseline (fig.1).

When air was replaced by nitrous oxide in oxygen before administration of fentanyl, MAP increased at carotid sinus perfusion pressures of 75, 100 and 125

Table 1 Systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures and heart rate (HR) at baseline and after administration of two different doses of fentanyl and naloxone (mean (SEM)). $^{*}P<0.05$. $^{**}P<0.01$ compared with baseline.†† $P<0.01$ compared with low-dose fentanyl

	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	HR (beat min^{-1})
Baseline	164.8 (4.8)	129.3 (7.2)	141.1 (3.2)	243.1 (11.5)
Low fentanyl	144.4 (8.9)*	105.0 (10.2)**	118.2 (9.4)**	263.6 (8.1)
High fentanyl	116.1 (5.1)**	81.6 (7.5)**	93.1 (6.4)**	226.6 (11.6)††
Naloxone	189.4 (11.2)**	146.3 (10.1)	160.6 (10.3)*	237.6 (6.5)

Table 2 Systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures and heart rate (HR) at baseline and after administration of two different doses of fentanyl during ventilation with air and ventilation with nitrous oxide (N_2O) and oxygen (O_2) (mean (SEM))

	SAP (mm Hg)		DAP (mm Hg)		MAP (mm Hg)		HR (beat min^{-1})	
	Air	N_2O–O_2	Air	N_2O–O_2	Air	N_2O–O_2	Air	N_2O–O_2
Baseline	167.9 (4.4)	175.0 (4.5)	133.1 (4.1)	139.8 (6.6)	144.6 (3.9)	151.5 (5.5)	233.3 (10.6)	248.8 (13.7)
Low fentanyl	144.4 (8.9)	149.3 (7.1)	105.0 (10.2)	114.0 (9.5)	118.2 (9.4)	125.8 (8.5)	263.6 (8.1)	273.0 (7.1)
High fentanyl	116.1 (5.1)	120.5 (6.4)	81.6 (7.5)	85.5 (7.7)	93.1 (6.5)	97.3 (7.1)	226.6 (11.6)	248.4 (5.5)

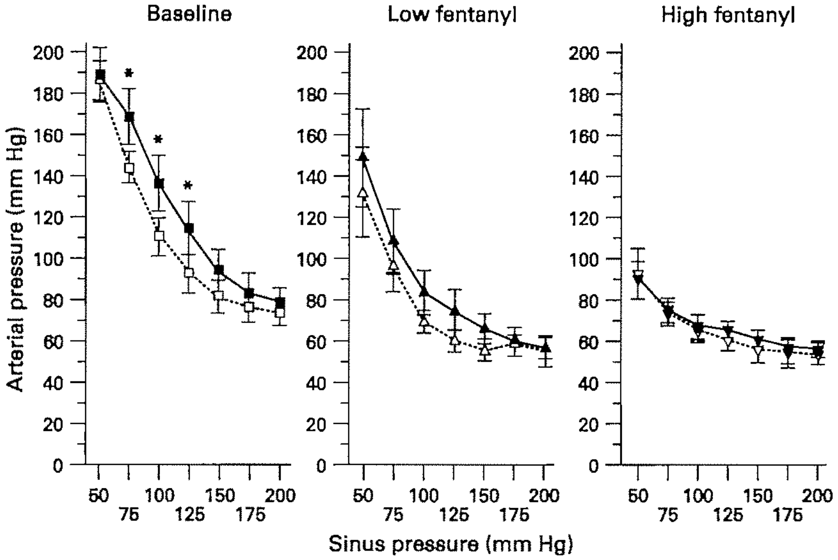

Figure 2 Baroreflex responses (systemic mean arterial pressure (MAP) *vs* carotid sinus perfusion pressure) in animals receiving either air (open symbols, interrupted lines) or nitrous oxide (filled symbols, solid lines) (mean, SEM). Panels show the following stages: baseline; low-dose fentanyl; high-dose fentanyl. $^*P<0.05$.

mm Hg (fig. 2), while baroreflex gain at 50–75 mm Hg decreased. HR responses were unchanged by nitrous oxide in oxygen (table 3).

After fentanyl, addition of nitrous oxide did not affect arterial pressures (fig. 2) or baroreflex gain. However, in the presence of fentanyl at the low and high doses, nitrous oxide in oxygen increased HR (ANOVA main effects; $P<0.05$ and $P<0.01$) (table 3).

Discussion

The aim of this study was to investigate the effect of generally used components of balanced anaesthesia, namely nitrous oxide and fentanyl, on high pressure baroreceptor reflex function. We used an animal experimental model which merits some comments on methodology.

First, we cut the vagus nerves to avoid secondary influences from cardiopulmonary low pressure reflexes[4,5]. As this procedure also denervates the baroreceptors of the aortic arch, only carotid baroreflex responses were evaluated. However, aortic baroreceptors primarily modulate high pressure responses[6,7] and thus are less likely to be significant for the overall cardiovascular reflex response to lowered arterial pressure, the object of this study. Second, the degree of baroreceptor activation depends on the carotid sinus perfusion pressure level and the velocity of the pulsatile pressure change. In our model, the profile of the pump-generated carotid sinus pressure wave differed from pressure waves normally produced by the pumping heart. This implies different baroreceptor activation compared with the intact animal at similar arterial pressure levels. However, the pulsatile characteristics of the pump-generated carotid pressure wave were essentially similar at each phase of the experiment, as pump rate was kept constant. Changes in carotid

Table 3 Heart rate (HR) at different carotid sinus perfusion pressures at baseline and after administration of fentanyl, nitous oxide (N_2O) and naloxone (mean (SEM))

	Carotid sinus perfusion pressure (mm Hg)						
	50	75	100	125	150	175	200
Baseline	249.1 (9.0)	236.1 (10.4)	217.4 (9.8)	201.4 (9.7)	193.8 (9.6)	189.6 (9.6)	186.1 (9.5)
Nitrous oxide	262.3 (8.9)	254.5 (10.8)	241.5 (12.0)	229.3 (12.5)	214.6 (9.9)	209.4 (9.3)	204.5 (10.8)
Baseline	253.4 (8.1)	241.8 (11.0)	228.0 (11.8)	217.6 (11.4)	210.4 (12.1)	201.5 (12.2)	195.6 (13.2)
Low fentanyl	263.6 (9.4)	254.5 (10.2)	236.1 (10.2)	223.6 (10.7)	210.4 (10.5)	207.5 (11.7)	201.6 (11.0)
Low fentanyl + N_2O	273.3 (8.1)	266.9 (7.1)	256.4 (6.7)	246.8 (7.3)	238.0 (9.1)	227.8 (7.5)	219.1 (7.6)
High fentanyl	225.4 (11.1)	215.9 (9.8)	205.0 (8.8)	198.1 (8.2)	189.1 (6.8)	183.0 (6.6)	180.8 (6.1)
High fentanyl + N_2O	244.9 (6.6)	237.4 (6.1)	228.4 (7.8)	217.1 (10.5)	210.0 (11.1)	204.0 (11.6)	197.9 (11.1)
Naloxone	270.6 (9.9)	257.9 (9.2)	235.0 (8.6)	224.7 (7.7)	211.1 (10.1)	197.1 (10.1)	199.5 (13.0)

sinus perfusion pressure were obtained by adjustments of the arteriovenous shunt in the extracorporeal circuit. This experimental perfusion design constitutes the basis for the comparisons in this study.

Nitrous oxide has been shown previously to increase systemic vascular resistance in combination with 1% halothane in humans[8] and in combination with pentobarbitone in dogs[9]. These findings, and other data in humans[10 11], indicate that nitrous oxide induces an increase in efferent sympathetic nervous activity (SNA). We observed circulatory effects (increased MAP) of nitrous oxide only when the carotid sinuses were perfused at pressures in the medium range (75–125 mm Hg). We suggest this reflects efficient baroreflex suppression of adrenergic nitrous oxide effects during intense baroreceptor activity (sinus perfusion pressure ≥150 mm Hg) and a background of pre-existing intense sympathetic outflow in the face of maximal baroreceptor unloading (sinus perfusion pressure <75 mm Hg). At these two extremes in sinus pressure, it is conceivable that nitrous oxide, although having sympatomimetic effects, adds only minimally to the prevailing degree of sympathetic discharge. These findings are in agreement with those of Bagshaw and Cox[12] in the dog during light halothane anaesthesia.

Fentanyl has been shown to reduce sympathetic and increase vagal neural tone[13–16]. These effects may depend on facilitation of impulse transmission at the dorsal nucleus of the vagus nerve and nucleus tractus solitarii of the baroreflex pathway[17 18]. However, the reduction in MAP produced by fentanyl throughout the sinus perfusion pressures used in our study, with vagotomized animals, indicated reduced sympathetic output or direct cardiovascular organ effects, or both. At low sinus perfusion pressures, we observed a dosedependent effect of fentanyl on MAP, probably reflecting the effects of fentanyl on the baroreflex as a dose-dependent reduction in baroreflex gain was observed at perfusion pressure increments of 50–125 mm Hg.

The effect of fentanyl on the baroreflex represents dose-dependent depression of baroreceptor arterial pressure control, as also shown in newborn infants[19]. Despite the fact that nitrous oxide attenuated the baroreceptor reflex, it did not further depress reflex control of arterial pressure when added to fentanyl at any of the infusion rates.

Data from this study support findings from other studies in humans[20] where resetting of the baroreflex has been found after fentanyl[19] and after the combination of fentanyl, diazepam and nitrous oxide[20]. Kortly and co-workers[20] also found that baroreflex control of heart rate was attenuated after lower doses of fentanyl (7.5 mg kg^{-1}). However, in their study and at higher doses of fentanyl (10 and 12.5 mg kg^{-1}) there was a discrepancy between baroreflexmediated tachycardia and bradycardia induced by lowered and increased arterial pressures compared with lower doses of fentanyl. This was postulated to be the result of enhanced vagal efferent activity mediated by fentanyl. In our study we did not find this difference in systemic arterial pressures or heart rate after low and high carotid sinus pressures, probably because we used vagotomized animals. However, species differences cannot be excluded. Furthermore, differences between human and nonerect walking animals in baroreceptor reflexes seem to apply mainly to low pressure cardiopulmonary receptors[21–24]. In our model these were excluded by vagotomy thus allowing for selective analysis of the high pressure carotid sinus part of the baroreceptor reflexes.

Naloxone was given to reverse the circulatory effects of fentanyl. After administration of naloxone, arterial pressure was not only restored but exceeded baseline arterial pressure. It is not clear from our study if this overshoot in arterial pressure reflected the central or peripheral effects of naloxone. Similar effects with naloxone have been observed in other studies. For example, in a study in conscious rabbits, naloxone increased arterial pressure both before and after sinoaortic barodenervation, but the increase was more pronounced after denervation. This indicates that the baroreceptor reflex buffers an increase in arterial pressure[25]. In other studies, naloxone has been shown to increase baroreflex sensitivity[26–29].

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References

1. Henriksson B-Å, Biber B, Martner J, Pontén J, Werner O. Cardiovascular studies during controlled baroreflex activation in the dog: I. Effects of enflurane. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 90–94.
2. Biber B, Martner J, Werner O. Modification by baroreceptor feedback of circulatory responses to noxious stimuli during anaesthesia in cats. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 391–395.
3. Scher AM. Carotid and aortic regulation of arterial blood pressure. *Circulation* 1977; **56**: 521–528.
4. Donald DE, Edis AJ. Comparison of aortic and carotid baroreflexes in the dog. *Journal of Physiology (London)* 1971; **215**: 521–538.
5. Pelletier CL, Shepherd JT. Circulatory reflexes from mechano-receptors in the cardioaortic area. *Circulation Research* 1973; **33**: 131–138.
6. Koike H, Mark AL, Heistad DD, Schmid PG. Influence of cardiopulmonary vagal afferent activity on carotid chemoreceptor and baroreceptor reflexes in the dog. *Circulation Research* 1975; **37**: 422–429.
7. Cox RH, Bagshaw RJ. Baroreceptor reflex control of arterial hemodynamics in the dog. *Circulation Research* 1975; **37**: 772–786.
8. Lundborg BO, Milde JH, Theye RA. Effect of nitrous oxide on myocardial contractility in dogs. *Canadian Anaesthetists Society Journal* 1966; **3**: 361–367.
9. Thorburn J, Smith G, Vance JP, Brown DM. Effect of nitrous oxide on the cardiovascular system and coronary circulation in the dog. *British Journal of Anaesthesia* 1979; **51**: 937–942.
10. Ebert TJ. Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. *Anesthesiology* 1990; **72**: 16–22.
11. Sellgren J, Pontén J, Wallin BG. Percutaneous recordings of muscle nerve sympathetic activity during propofol, nitrous oxide and isoflurane anesthesia in man. *Anesthesiology* 1990; **73**: 20–27.
12. Bagshaw RJ, Cox RH. Nitrous oxide and the baroreceptor reflexes in the dog. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 31–38.
13. Laubie M, Schmitt S, Canellas J, Roquebert P, Demichel P. Centrally mediated bradycardia and hypotension induced by narcotic analgesics: dextromoramide and fentanyl. *European Journal of Pharmacology* 1974; **28**: 66–75.
14. Daskalopoulos N, Laubie M, Schmitt H. Localization of the central sympatho-inhibitory effect of a narcotic analgesic agent, fentanyl in cats. *European Journal of Pharmacology* 1975; **33**: 91–97.

15. Laubie M, Schmitt S, Drouillet M. Central sites and mechanisms of the hypotensive and bradycardic effects of narcotic analgesic agent fentanyl. *Naunyn-Schmiedebergs Archives of Pharmacology* 1977; **296**: 255–261.
16. Taneyama C, Goto H, Kohmo N, Benson KT, Sasao J, Arakawa K. Effects of fentanyl, diazepam and the combination of both on arterial baroreflex and sympathetic nerve activity in intact and barodenervated dogs. *Anesthesia and Analgesia* 1993; **77**: 44–48.
17. Laubie M, Schmitt S. Action of the morphinometic agent fentanyl, on the nucleus tractus solitarii and the nucleus ambiguus cardiovascular neurones. *European Journal of Pharmacology* 1980; **67**: 403–412.
18. Gordon FJ. Opioids and central baroreflex control; a site of action in the nucleus tractus solitarius. *Peptides* 1990; **11**: 305–309.
19. Murat I, Levron JC, Berg A, Saint-Maurice C. Effects of fentanyl on baroreceptor reflex control of heart rate in newborn infants. *Anesthesiology* 1988; **68**: 717–722.
20. Kortly KJ, Ebert TJ, Vucins EJ, Roerig DL, Stadnicka A, Kampine JP. Effects of fentanyl–diazepam–nitrous oxide anaesthesia on arterial baroreflex control of heart rate in man. *British Journal of Anaesthesia* 1986; **58**: 406–414.
21. Selldén H, Sjövall H, Ricksten SE. Sympathetic nerve activity and central haemodynamics during mechanical ventilation with positive end-expiratory pressure in rats. *Acta Physiologica Scandinavica* 1986; **127**: 51–60.
22. Selldén H, Delle M, Sjövall H, Ricksten SE. Reflex changes in sympathetic nerve activity during mechanical ventilation with PEEP in sino-aortic denervated rats. *Acta Physiologica Scandinavica* 1987; **130**: 15–24.
23. Selldén H, Sjövall H, Wallin BG, Häggendal J, Ricksten SE. Changes in muscle sympathetic nerve activity, venous plasma catecholamines and calf vascular resistance during mechanical ventilation with PEEP in humans. *Anesthesiology* 1989; **70**: 243–250.
24. Takeshita A, Mark AL, Eckberg DL, Abboud FM. Effect of central venous pressure on arterial baroreflex control of heart rate. *American Journal of Physiology* 1979; **236**: H42–H47.
25. Schadt JC, Gaddis RR. Cardiovascular responses to hemorrhage and naloxone in conscious barodenervated rabbits. *American Journal of Physiology* 1986; **251**: R909–R915.
26. Koyama S, Manugian V, Ammons WS, Santiesteban HL, Manning JW. Effect of naloxone on baroreflex, sympathetic tone and arterial pressure in the cat. *European Journal of Pharmacology* 1983; **90**: 367–376.
27. Petty MA, Reid JL. The effect of opiates on arterial baroreceptor reflex function in the rabbit. *Naunyn-Schmiedebergs Archives of Pharmacology* 1982; **319**: 206–211.
28. Szilagyi JE. Endogenous opiate modulation of baroreflexes in normotensive and hypertensive rats. *American Journal of Physiology* 1988; **255**: H987–H991.
29. Schobel HP, Oren RM, Mark AL, Ferguson DW. Naloxone potentiates baroreflex sympathetic control in normal humans. *Circulation Research* 1992; **70**: 172–183.

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Effect of sevoflurane anaesthesia on plasma concentrations of glutathione S-transferase

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Summary

To assess the effect of sevoflurane anaesthesia on hepatocellular integrity, we measured plasma concentrations of glutathione S-transferase (GST) before anaesthesia and 1, 3, 6 and 24 h after the end of anaesthesia in 41 healthy, Japanese patients undergoing elective, body surface surgery. Sevoflurane (approximately 1.0 MAC) was delivered in 50–66% nitrous oxide in oxygen via a circle system, with a fresh gas flow of 6 litre min^{-1}. Ventilation was spontaneous in all patients. Mean duration of anaesthesia was 101 min. Concentrations of GST increased significantly 1 h after the end of anaesthesia (P=0.0075), but this was not significantly different from preoperative concentrations at 3, 6 and 24 h. Three patients developed a large secondary increase in GST concentrations at 24 h. The increase observed at 1 h was probably a result of reduced total liver blood flow; the mechanism for the secondary increase at 24 h is unclear but the possibility that products of sevoflurane biotransformation are responsible cannot be excluded. (*Br. J. Anaesth.* 1996;**77**:404–407)

Key words

Anaesthetics volatile, sevoflurane. Toxicity, hepatic. Enzymes, glutathione S-transferase.

Sevoflurane is a relatively new inhalation anaesthetic agent which has recently been licensed for clinical use in the UK[1]. It undergoes more biotransformation than isoflurane and enflurane[2], although its low blood-gas solubility coefficient and rapid elimination are thought to preclude prolonged elevated concentrations of metabolites and resultant organ dysfunction[3–5]. Studies investigating hepatic function after sevoflurane anaesthesia in humans would tend to support this view[3 4 6 7], although there are at least four case reports of sevoflurane-associated hepatotoxicity in the Japanese literature[8–11]. Standard biochemical tests of liver function however, have limited use in the detection of minor degrees of anaesthetic-related liver dysfunction. In contrast, measurement of glutathione S-transferase (GST) concentration in plasma provides a highly specific test of hepatocellular damage, and GST results correlate better with histological changes than do the aminotransferases[12]. GST concentrations increase transiently after anaesthesia with halothane[13–17] and enflurane[13] but not after isoflurane[13 14 17 18] or propofol[18 19]; the frequency of abnormal GST concentrations observed after halothane, enflurane and isoflurane anaesthesia correlates directly with the extent of metabolism and incidence of reported clinical hepatic dysfunction for these agents[13]. More recently, GST concentrations have been found to increase after sevoflurane anaesthesia in children[20], although experience with the particular GST assay used is limited.

We have measured GST concentrations in adult patients undergoing anaesthesia with sevoflurane to assess its effect on hepatocellular integrity.

Patients and methods

After obtaining approval from the Ethics Committee of Juntendo University, written informed consent was obtained from 50 healthy, Japanese patients, ASA I or II, undergoing elective general anaesthesia for body surface surgery which was expected to last 1–3 h. Exclusion criteria included obesity (body weight >20% above ideal weight), excessive alcohol intake (>3 u. day^{-1}), previous liver disease or exposure to general anaesthesia in the preceding 3 months. Patients receiving medications likely to interfere with liver function were also excluded.

Premedication was not given. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} i.v. in a dose sufficient to abolish the eyelash reflex, and suxamethonium 1 mg kg^{-1} i.v. was given to facilitate tracheal intubation if necessary. Anaesthesia was maintained with approximately 1.0 MAC of sevoflurane and 50–66% nitrous oxide in oxygen (sevoflurane MAC in 65% nitrous oxide: 1.4% for patients aged 25 yr, 1.1% for patients aged 40 yr, 0.87% for patients aged 60 yr [data on file, Abbott Laboratories]). Patients breathed spontaneously from a circle system delivered with a fresh gas flow rate of 6 litre min^{-1}; the carbon dioxide absorbent used was soda lime (Dragersorb 800, Drager, Germany). End-tidal concentrations of sevoflurane and carbon dioxide (Datex Capnomac AGM-103-30-00, Helsinki, Finland) were measured continuously throughout anaesthesia. The total dose of sevoflurane administered to each patient was calculated in MAC hours. Pentazocine was used for analgesia after surgery if required.

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LABORATORY ANALYSIS

Blood was sampled immediately before induction of anaesthesia (time 0), and 1, 3, 6 and 24 h after the end of anaesthesia for measurement of plasma GST B_1 concentration by specific radioimmunoassay, as described previously[21]. All samples from the same subject were measured in the same assay run. Inter- and intra-assay coefficients of variation were <10% and <5%, respectively, over the range 2–25 µg litre^{-1}. The reference range for GST concentration is 0.5–4.8 µg litre^{-1}.

STATISTICAL ANALYSIS

Data were analysed by Friedman's two-way analysis of variance for repeated measurements. The Wilcoxon signed rank test was used to examine changes in GST concentration from time 0 to 1, 3, 6 and 24 h after induction of anaesthesia. $P<0.05$ was taken as significant. Analysis was performed with Minitab for Windows (version 10.2) run on a Dell Dimension computer.

Results

Of the 50 patients studied, nine were excluded from analysis; three patients needed to be paralysed and their lungs ventilated for surgical requirements, and six were administered extradural anaesthesia in addition to general anaesthesia. Data from the remaining 41 patients (27 male; mean age 42 (range 18–67) yr) were analysed. This sample size gave the study a power of 76% for a change in GST concentration of >0.5 µg litre^{-1}.

Thirty of these patients underwent minor or intermediate eye, nose or throat surgery; the remainder underwent relatively minor orthopaedic surgery such as arthroscopy. Forty patients received suxamethonium to facilitate tracheal intubation. The mean dose of thiopentone given for induction of anaesthesia was 263 (SD 39) mg and the mean sevoflurane dose administered for maintenance was 1.73 (range 0.59–3.18) MAC h. Mean duration of anaesthesia was 101 (45–155) min. Significant temporal changes in GST concentrations occurred after anaesthesia ($P<0.001$). Plasma GST concentrations increased significantly 1 h after the end of anaesthesia from time 0 ($P=0.0075$), but these were not significantly different from preoperative concentrations at 3, 6 and 24 h (table 1, fig. 1).

Although GST concentrations were still increased at 3 h this was not statistically significant ($P=0.069$). Ten patients had GST concentrations >4.8 µg litre^{-1} in blood samples obtained before anaesthesia; the overall pattern of GST changes after anaesthesia in these patients was similar to that in patients who had GST concentrations <4.9 µg litre^{-1} before anaesthesia. Three of these 10 patients had GST concentrations >4.8 µg litre^{-1} only in the sample obtained before anaesthesia. Three patients (7%) with preoperative GST concentrations within the reference range developed a large secondary increase in GST concentrations at 24 h (table 2). Seven of the 31 patients (23%) with preoperative GST concentrations <4.8 µg litre^{-1} developed an increased GST concentrations at some time during the study. No patient developed hypotension (mean arterial pressure <70% of pre-induction level), arterial oxygen saturation <94% or end-tidal carbon dioxide concentration >8 kPa at any time during anaesthesia.

Table 1 Median (1st, 3rd quartiles) glutathione S-transferase concentrations (µg litre^{-1}) in 41 patients receiving sevoflurane anasthesia. $^*P < 0.01$ compared with concentrations before anaesthesia

Before anaesthesia	1 h	3 h	6 h	24 h
2.8	3.9*	3.5	2.8	3.3
(2.0, 5.0)	(2.6, 5.3)	(2.6, 5.2)	(2.1, 3.8)	(1.6, 4.6)

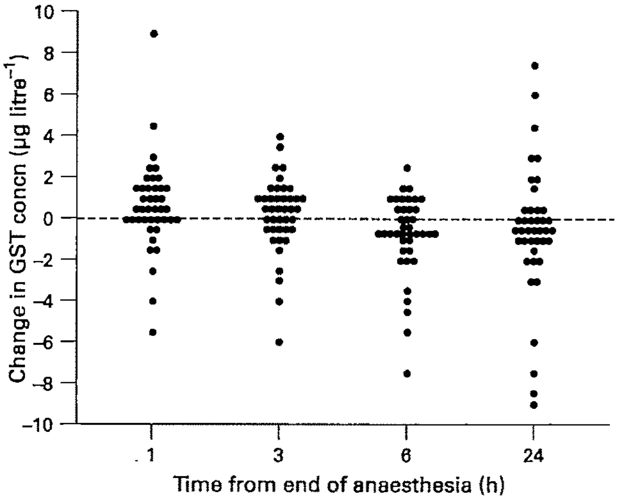

Figure 1 Individual changes in plasma gluthathione S-transferase (GST) concentrations from the preoperative sample.

Discussion

The results of this study suggest that sevoflurane influences plasma concentrations of GST after anaesthesia, confirming previous findings in children[20]. GST concentrations increased significantly from preoperative values 1 h after the end of anaesthesia, were still increased at 3 h and had decreased to preoperative concentrations at 6 and 24 h. We have demonstrated previously that GST concentrations increase 3 and 6 h after anaesthesia with halothane[13–16] and enflurane[15] but not after isoflurane[13 14]. Other workers have confirmed that GST concentrations increase after halothane but not after isoflurane anaesthesia[17] and have also demonstrated no change after propofol anaesthesia[18 19]. Reduced liver blood flow is believed to be responsible for these increases; alternative explanations such as variation in GST concentration throughout the day or reduced clearance of GST have been discounted previously[22]. Several studies have shown that sevoflurane has little overall effect on hepatic blood flow in experimental animals[23–26], although if hepatic arterial

Table 2 Plasma concentrations of glutathione S-transferase (µg litre^{-1}) in patients who developed a large secondary increase at 24 h

Before anaesthesia	1 h	3 h	6 h	24 h
1.4	2.6	2.6	2.8	7.3
2.8	4.9	4.4	4.0	10.2
4.7	6.3	7.2	5.8	9.4

flow is compromised there may be a smaller margin of safety against hypoxia with sevoflurane compared with halothane and isoflurane[27]. There is evidence in humans to suggest that sevoflurane reduces total hepatic blood flow[28], although this has not been confirmed by other workers[29,30]. Our findings appear to support the view that sevoflurane reduces hepatic blood flow in humans.

Three patients (7%) developed a much larger secondary increase in GST concentrations at 24 h. In a previous study, 18% of patients anaesthetized with halothane and 10% of those who received enflurane developed similar increases at 24 h; this later increase did not occur in patients after isoflurane anaesthesia[13]. The mechanism for these increases at 24 h is unclear but the possibility that products of biotransformation (including those of sevoflurane) are responsible cannot be excluded. The overall extent of sevoflurane metabolism in humans is approximately 5%[23], resulting in the formation of hexafluoroisopropanol (HFIP) and fluoride ion. Neither of these products is likely to be responsible for initiating hepatic damage[5]. Sevoflurane reacts with carbon dioxide absorbents resulting in generation of breakdown products. Five degradation products have been identified *in vitro*[31], although only compound A (and to a lesser extent compound B) is produced under conditions likely to be encountered clinically. Factors which alter the concentration of compound A include fresh gas flow, temperature of the soda lime and concentration of sevoflurane in the circle system. Low fresh gas flows are associated with an increase in temperature of the soda lime and increased concentrations of compound A which increase further with prolonged anaesthesia[32,33]. In this study, a fresh gas flow of 6 litre min^{-1} was used to prevent the build up of a significant concentration of compound A. While there is debate about the potential for compound A to induce renal damage, there is no suggestion that it may initiate hepatic damage[34]. We do not believe that compound A is responsible for the observed increase in GST concentration.

The reference range for GST concentration in adult patients in the UK is 0.5–4.8 µg litre^{-1}; the range for the Japanese population is not known. As 10 patients (20%) in this study had preoperative GST concentrations >4.8 µg litre^{-1}, it could be argued that there is a different reference range for Japanese patients. However, the pattern of GST response after anaesthesia was similar if these patients were excluded from analysis, and therefore the overall conclusion from this study is unaltered. Three of these 10 patients had GST concentrations > 4.8 µg litre^{-1} in the preoperative sample only, suggesting that in these patients increased GST concentrations may have resulted from fasting, as has been described previously[22].

We conclude that sevoflurane anaesthesia is associated with a transient increase in plasma GST concentrations after anaesthesia, reflecting a minor degree of impaired hepatocellular integrity. Some patients develop increased GST concentrations 24 h after sevoflurane anaesthesia; the reasons for this secondary increase are unclear and require further investigation.

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References

1. Smith I, Nathanson M, White PF. Sevoflurane—a long-awaited volatile anaesthetic. *British Journal of Anaesthesia* 1996; **76**: 435–445.
2. Kharasch ED, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition. 1. Sevoflurane and metabolite pharmacokinetics. *Anesthesiology* 1995; **82**: 1369–1378.
3. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. *Anesthesiology* 1981; **54**: 100–106.
4. Frink EJ, Ghantous H, Malan TP, Morgan S, Fernando J, Gandolfi AJ, Brown BR. Plasma inorganic flouride with sevoflurane anesthesia: correlation with indices of hepatic and renal function. *Anesthesia and Analgesia* 1992; **74**: 231–235.
5. Frink EJ. The hepatic effects of sevoflurane. *Anesthesia and Analgesia* 1995; **81**: S46–S50.
6. Bito H, Ikeda K. Closed-circuit anesthesia with sevoflurane in humans. Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. *Anesthesiology* 1994; **80**: 71–76.
7. Bito H, Ikeda K. Renal and hepatic function in surgical patients after low-flow sevoflurane or isoflurane anesthesia. *Anesthesia and Analgesia* 1996; **82**: 173–176.
8. Watanabe K, Hatakenaka S, Ikemune K, Chigyo Y, Kubozono T, Arai T. A case of suspected liver dysfunction induced by sevoflurane anaesthesia. *Masui* 1993; **42**: 902–905.
9. Shichinohe Y, Masuda Y, Takahashi H, Kotaki M, Omote T, Shichinohe M, Namiki A. A case of postoperative hepatic injury after sevoflurane anaesthesia. *Masui* 1992; **41**: 1802–1805.
10. Ogawa M, Doi K, Mitsufuji T, Satoh K, Takatori T. Drug induced hepatitis following sevoflurane anaesthesia in a child. *Masui* 1991; **40**: 1542–1545.
11. Kayashima K, Matsumoto T, Sata T, Shigematsu A. A case of severe liver dysfunction after sevoflurane anaesthesia. *Rinsho Masui* 1995; **19**: 53–55.
12. Sherman M, Bass NM, Campbell JAH, Kirsch RE. Radioimmunoassay of human ligandin. *Hepatology* 1983; **3**: 162–169.
13. Hussey AJ, Aldridge LM, Paul D, Ray DC, Beckett GJ, Allan LG. Plasma glutathione Stransferase concentration as a measure of hepatocellular integrity following a single general anaesthetic with halothane, enflurane or isoflurane. *British Journal of Anaesthesia* 1988; **60**: 130–135.
14. Allan LG, Hussey AJ, Howie J, Beckett GJ, Smith AF, Hayes JD, Drummond GB. Hepatic glutathione S-transferase release after halothane anaesthesia: open randomised comparison with isoflurane. *Lancet* 1987; **1**: 771–774.
15. Ray DC, Beckett GJ, Hayes JD, Drummond GB. Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia. *British Journal of Anaesthesia* 1989; **62**: 553–559.
16. Ray DC, Howie AF, Beckett GJ, Drummond GB. Preoperative cimetidine does not prevent subclinical halothane hepatotoxicity in man. *British Journal of Anaesthesia* 1989; **63**: 531–535.
17. Murray JM, Rowlands BJ, Trinick TR. Indocyanine green clearance and hepatic function during and after prolonged anaesthesia: comparison of halothane with isoflurane. *British Journal of Anaesthesia* 1992; **68**: 168–171.
18. Murray JM, Phillips AS, Fee JPH. Comparison of the effects of isoflurane and propofol on hepatic glutathione S-transferase concentrations during and after prolonged anaesthesia. *British Journal of Anaesthesia* 1994; **72**: 599–601.
19. Murray JM, Trinick TR. Hepatic function and indocyanine green clearance during and after prolonged anaesthesia with propofol. *British Journal of Anaesthesia* 1992; **69**: 643–644.
20. Taivainen T, Tiainen P, Meretoja OA, Raiha L, Rosenberg PH. Comparison of the effects of sevoflurane and halothane on the quality of anaesthesia and serum glutathione S-transferase alpha and fluoride in paediatric patients. *British Journal of Anaesthesia* 1994; **73**: 590–595.
21. Beckett GJ, Hayes JD. Development of specific radioimmunoassays for the measurement of human hepatic basic and N/A2b glutathione S-transferase. *Clinica Chimica Acta* 1984; **141**: 267–273.

22. Ray DC, Aldridge LM, Spens HJ, Drummond GB, Howie AF, Beckett GJ. Biological variation and the effect of fasting and halothane anesthesia on plasma glutathione S-transferase concentrations. *Clinical Chemistry* 1995; **41**: 668–671.
23. Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia with and without 50% nitrous oxide. *Journal of Pharmacology and Experimental Therapeutics* 1984; **231**: 640–648.
24. Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messner K. Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. *Anesthesia and Analgesia* 1992; 74: 79–88.
25. Frink EJ, Morgan SE, Coetzee A, Conzen PF, Brown BR. The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs. *Anesthesiology* 1992; **76**: 85–90.
26. Bernard J-M, Doursout M-F, Wouters P, Hartley CJ, Merin RG, Chelly JE. Effects of sevoflurane and isoflurane on hepatic circulation in the chronically instrumented dog. *Anesthesiology* 1992; **77**: 541–545.
27. Fujita Y, Kimura K, Hamada H, Takaori M. Comparative effects of halothane, isoflurane, and sevoflurane on the liver with hepatic artery ligation in the beagle. *Anesthesiology* 1991; **75**: 313–318.
28. Hongo T. Sevoflurane reduced but isoflurane maintained hepatic blood flow during anesthesia in man. *Journal of Anesthesia* 1994; **8**: 55–59.
29. Kanaya N, Nakayama M, Fujita S, Namiki A. Comparison of the effects of sevoflurane, isoflurane and halothane on indocyanine green clearance. *British Journal of Anaesthesia* 1995; **74**: 164–167.
30. Kobayashi M. The effects of sevoflurane and isoflurane on hepatic blood flow in man. *Masui* 1996; **45**: 281–286.
31. Hanaki C, Fujii K, Morio M, Tashima T. Decomposition of sevoflurane by soda lime. *Hiroshima Journal of Medical Science* 1987; **36**: 61–67.
32. Fang ZX, Eger EI. Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and baralyme in a standard anesthetic circuit. *Anesthesia and Analgesia* 1995; **81**: 564–568.
33. Bito H, Ikeda K. Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. *British Journal of Anaesthesia* 1995; 74: 667–669.
34. Eger EI, Martin JL, Tinker JH. The safety of sevoflurane has not been adequately established. *Anesthesia and Analgesia* 1996; **82**: 431–432.

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Normovolaemic haemodilution attenuates cardiac depression induced by sodium bicarbonate in canine metabolic acidosis[†]

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Summary

This study was designed to determine if coexisting metabolic acidosis or normovolaemic haemodilution, or both, modifies the acute cardiodepressant effect of i.v. sodium bicarbonate. Thirty-one mongrel dogs were anaesthetized with halothane, and the lungs ventilated mechanically; dogs were allocated randomly to one of four groups: control group (pHa 7.39 (SD 0.03), base excess −1.0 (1.6) mmol litre^{-1}, haemoglobin 13.9 (2.5) g dl^{-1} (n=8)), metabolic acidosis group (pHa 7.21 (0.05), base excess −11.2 (2.1) mmol litre^{1}, haemoglobin 13.4 (2.6) g dl^{-1} (n=8)), anaemia group (pHa 7.40 (0.04), base excess 0.1 (2.0) mmol litre^{-1}, haemoglobin 7.2 (1.1) g dl^{-1} (n=8)) or anaemia acidosis group (pHa 7.22 (0.04), base excess −11.0 (2.2) mmol litre^{-1}, haemoglobin 7.4 (0.3) g dl^{-1} (n=7)). Metabolic acidosis was induced by continuous i.v. infusion of hydrochloric acid 2 mol litre^{-1}. Normovolaemic haemodilution was undertaken by phlebotomy and simultaneous exchange with lactated Ringer's solution at 37 °C. Mean arterial pressure (MAP), pulmonary artery pressure, right atrial pressure (RAP), maximum rate of change of pressure in the right ventricle (RV dP/dtmax) and pulmonary blood flow (PBF) were measured at 30 s, 1 and 3 min after administration of 7% sodium bicarbonate solution 1 mmol kg^{-1} given into the right atrium over 5 s. Sodium bicarbonate produced significant decreases in MAP and RV dP/dtmax at 30 s in all groups except for the anaemia acidosis group ($P<0.05$). There was a significant decrease in right ventricular stroke volume in the metabolic acidosis group from baseline values ($P<0.05$), and compared with the three other groups ($P<0.05$). These results indicate that the cardiodepressant effect of sodium bicarbonate 1 mmol kg^{-1} i.v. during metabolic acidosis was more pronounced than without acidosis, but was attenuated in the presence of normovolaemic haemodilution. (*Br. J. Anaesth.* 1996;**77**:408–412)

Key words

Acid–base equilibrium, metabolic acidosis. Acid-base equilibrium, respiratory acidosis. Complications, hypercapnia. Pharmacology, sodium bicarbonate. Dog.

Massive haemorrhage and systemic hypotension treated by replacement with crystalloid solution are frequently accompanied by metabolic acidosis and haemodilution. Although administration of sodium bicarbonate may be considered in these situations, it may reduce peripheral oxygen availability by increaseing extracellular pH[1] and produce paradoxical intracellular acidosis by free diffusion of carbon dioxide liberated from bicarbonate[2,3]. Depression of cardiac performance and peripheral vascular dilatation as a result of paradoxical intracellular acidosis have been implicated in circulatory alterations after bicarbonate administration[4]. A combination of these effects has detrimental consequences both metabolically and haemodynamically[5,6]. A recent study has demonstrated that maximum depression of cardiac performance by bicarbonate is more pronounced during metabolic acidosis than without acidosis in *in vivo* canine preparations[7].

When normovolaemia is maintained, progressive anaemia causes a modest increase in cardiac output with little change in arterial pressure and heart rate (HR) in both humans[8,9] and animals[10–12]. Systemic vascular resistance is decreased because of peripheral vascular dilatation secondary to anaemia. The pharmacologically depressed myocardium has diminished ability to increase cardiac output in response to haemodilution[10]. How augmentation of cardiac output in response to haemodilution is modified by the presence of metabolic acidosis is unknown. In addition, the effects of coexisting metabolic acidosis and normovolaemic haemodilution on myocardial depression produced by sodium bicarbonate have not been examined.

This study was designed in an *in vivo* canine preparation to assess the effects of normovolaemic haemodilution on the acute cardiovascular effects of sodium bicarbonate at physiological arterial pH (pHa) and with metabolic acidosis at a pHa value of approximately 7.2.

Materials and methods

The study was approved by our institutional Animal Care Committee. We studied 32 adult mongrel dogs of both sexes, weighing 10.5–15 kg. All dogs were

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anaesthetized with thiamylal 15 mg kg^{-1} and the trachea intubated. The lungs were ventilated mechanically with room air supplemented with oxygen via a cuffed tracheal tube, using a volume-cycled animal ventilator (model R-60, Aika Co., Ltd, Tokyo, Japan). End-tidal halothane concentrations were measured continuously (Capnomac Ultima, Datex, Helsinki, Finland) and maintained at 0.65–0.75%. Suxamethonium 20 mg was given i.v. at the time of tracheal intubation followed by 10 mg h^{-1} thereafter to produce neuromuscular block. During all measurements, pulmonary arterial blood temperature was maintained at 35.8–38.0 °C. Lactated Ringer's solution was administered at a constant rate of 10 ml kg^{-1} h^{-1} during surgical preparation and equilibration period, followed by 5 ml kg^{-1} h^{-1} during haemodynamic measurements.

An i.v. cannula was inserted into a forelimb vein for administration of lactated Ringer's solution. Lead II of the electrocardiogram (model 2236A, NEC San-ei Instruments Co., Ltd, Tokyo, Japan) was monitored continuously using subcutaneous electrodes. HR was measured on a beat-to-beat basis by a cardiotachometer (model 1321, NEC San-ei Instruments Co., Ltd, Tokyo, Japan) triggered by lead II of the electrocardiogram. Measurement of arterial pressure and blood sampling for blood-gas analysis and measurement of haemoglobin concentration (288 Blood Gas System, Ciba-Corning, Medfield, MA, USA) were performed via the femoral arterial catheter. A flow-directed, balloon-tipped pulmonary artery catheter (5Fr Thermodilution Catheter, Arrow, Reading, PA, USA) was inserted via the femoral vein to permit continuous monitoring of pulmonary artery pressure. Another catheter was positioned in the right atrium from the contralateral femoral vein for monitoring right atrial pressure (RAP). A 5-French gauge catheter-tipped transducer (model MPC-500, Miller Instruments Inc., Houston, TX, USA) was inserted via the right external jugular vein and positioned in the right ventricle to obtain maximum rate of change of pressure in the right ventricle (RV d*P*/d*t*max) using a differential amplifier (model 1323, NEC San-ei Instruments Co., Ltd, Tokyo, Japan).

After the pulmonary trunk was dissected free of the surrounding tissue through a left-sided thoracotomy in the fourth intercostal space, an electromagnetic flow probe of appropriate size (model FR 12–16 mm, Nihon-Koden Co., Ltd, Tokyo, Japan) was placed around the pulmonary trunk for continuous measurement of pulmonary blood flow (PBF). The flow probe was calibrated with 0.9% saline solution *in vitro* before implantation, and PBF was measured continuously with a square-wave electromagnetic blood flowmeter (model MFV-3200, NihonKoden Co., Ltd, Tokyo, Japan). All recordings were made on an eight-channel recorder (model Recti-Horiz-8K, NEC San-ei Instruments Co., Ltd, Tokyo, Japan).

The dogs were allocated randomly to one of four groups: control (*n*=8), metabolic acidosis (*n*=8), anaemia (*n*=8) or anaemia acidosis (*n*=8). After a stabilization period of at least 2 h after the surgical procedures, in the control group (Pa_{CO_2} 4.9–5.7 kPa and base excess > −3 mmol $litre^{-1}$) 7% sodium bicarbonate solution 1 mmol kg^{-1} (1.2 ml kg^{-1}) was given into the right atrium over 5 s, and haemodynamic variables were recorded continuously for 3 min. Ventilator settings were kept constant during these measurements.

Metabolic acidosis of base deficit less than −8 mmol $litre^{-1}$ was induced and maintained in the metabolic acidosis group by continuous infusion of hydrochloric acid 2 mol $litre^{-1}$ at an approximate rate of 10–15 ml h^{-1}, while Pa_{CO_2} was maintained at 4.9–5.7 kPa. After a stabilization period of at least 2 h, after establishment of the target metabolic acidosis, 7% sodium bicarbonate solution 1 mmol kg^{-1} (1.2 ml kg^{-1}) was given into the right atrium over 5 s, and the same haemodynamic measurements made.

The anaemia and anaemia acidosis groups were treated similarly to the control and metabolic acidosis groups except that normovolaemic haemodilution was produced to obtain haemoglobin concentrations of 7–7.5 g dl^{-1}. Normovolaemia was produced by phlebotomy and simultaneous exchange with lactated Ringer's solution at 37 °C in a ratio of approximately 1:3 aided by the stability of pulmonary artery occlusion pressure (PAOP). In the anaemia acidosis group, haemodilution preceded metabolic acidosis.

All values are expressed as mean (SD). Both mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were obtained by electronic integration of pulse pressure. Right ventricular stroke volume (RVSV) was calculated as PBF divided by HR. Analysis of changes in haemodynamic variables from baseline (30 s, 1 and 3 min) and comparison of data between the four groups (baseline values and maximum changes from baseline) were performed using one-way and two-way ANOVA, respectively, followed by the Student's *t* test with Bonferroni's correction. $P<0.05$ was considered the minimum level of statistical significance.

Results

One dog from the anaemia acidosis group died before completing the study and only data from the remaining 31 dogs were analysed. Mean values of pHa and base excess in the metabolic acidosis and anaemia acidosis groups were significantly lower than those in the control and anaemia groups, whereas there were no differences in Pa_{CO_2} and Pa_{O_2} values between the groups (table 1). Haemoglobin concentrations in the anaemia and anaemia acidosis groups were significantly lower than those in the control and metabolic acidosis groups (table 1). There were no differences in plasma electrolyte concentrations between the groups (table 1).

There were no differences in PAOP values before and after haemodilution, immediately before administration of sodium bicarbonate in the anaemia group (6.5 (3.2) *vs* 6.7 (3.3) mm Hg, respectively) and in the anaemia acidosis group (5.4 (0.9) *vs* 5.2 (1.3) mm Hg, respectively). Before administration of sodium bicarbonate, PBF in the anaemia acidosis group was significantly greater than in the control group ($P<0.05$, table 2). Similarly, RVSV in the anaemia acidosis group was significantly greater than that in the control and metabolic acidosis groups ($P<0.05$, table 2). Compared with baseline values, administration of 7% sodium bicarbonate 1.2 ml kg^{-1} produced consistent but transient increases in RAP in all groups ($P<0.05$, table 2). Transient but signifi-

Table 1 Arterial blood-gas values and electrolyte and haemoglobin concentrations (mean (SD)). $^*P < 0.05$ *vs* control and anaemia groups. $^\dagger P < 0.05$ *vs* control and metabolic acidosis groups

	Group			
	Control (*n*=8)	Metabolic acidosis (*n*=8)	Anaemia (*n*=8)	Anaemia acidosis (*n*=7)
Arterial blood-gas				
pHa	7.39 (0.03)	7.21 (0.05)*	7.40 (0.04)	7.22 (0.04)*
Pa_{CO_2} (kPa)	5.2 (0.4)	5.4 (0.4)	5.3 (0.3)	5.2 (0.1)
Pa_{O_2} (kPa)	15.8 (3.7)	14.2 (4.1)	19.7 (4.9)	17.3 (5.3)
Base-excess (mmol litre^{-1})	−1.0 (1.6)	−11.2 (2.1)*	0.1 (2.0)	−11.0 (2.2)*
Electrolytes				
Na (mmol litre^{-1})	147 (5)	146 (5)	144 (5)	145 (5)
K (mmol litre^{-1})	3.0 (0.5)	3.2 (0.5)	3.4 (0.3)	3.4 (0.7)
Ca^{2+} (mmol litre^{-1})	1.2 (0.1)	1.2 (0.1)	1.1 (0.1)	1.1 (0.1)
Haemoglobin (g dl^{-1})	13.9 (2.5)	13.4 (2.6)	7.2 (0.2)†	7.4 (0.3)†

Table 2 Baseline haemodynamic values and percentage change in haemodynamic responses to bolus injection of sodium bicarbonate 1 mmol kg^{-1} (mean (SD)). $^*P < 0.05$ *vs* control and metabolic acidosis groups. $^\dagger P < 0.05$ *vs* control, anaemia and anaemia acidosis groups. $^\ddagger P < 0.05$ *vs* control group. $^\S P < 0.05$ *vs* baseline values; MAP = Mean arterial pressure (mm Hg); HR = Heart rate (beat min^{-1}); MPAP = Mean pulmonary artery pressure (mm Hg); RAP = Right atrial pressure (mm Hg); RV d*P*/d*t*max = Maximum rate of change of pressure in the right ventricle (mm Hg s^{-1}); PBF = Pulmonary blood flow (litre min^{-1}); RVSV = Right ventricular stroke volume (ml)

	Time after injection			
	Baseline	30 s	1 min	3 min
Control group (*n*=8)				
MAP	97 (23)	−13.5 (5.5)§	1.1 (4.7)	2.8 (2.3)
HR	119 (24)	2.9 (6.0)	2.8 (2.4)	2.0 (3.7)
MPAP	14.3 (3.4)	0.9 (6.0)	5.9 (6.7)	3.8 (5.2)
RAP	1.3 (1.0)	185 (169)§	120 (132)§	31 (41)
RV d*P*/d*t*max	590 (117)	−12.5 (9.8)§	−8.9 (5.7)§	3.3 (6.0)
PBF	1.41 (0.21)	8.4 (7.9)	8.4 (6.0)§	10.1 (5.9)§
RVSV	12.2 (2.4)	5.6 (4.6)	6.5 (5.8)	8.0 (7.1)§
Metabolic acidosis group (*n*=8)				
MAP	80 (19)	−9.7 (7.9)§	−1.2 (14.4)	6.7 (5.4)§
HR	131 (20)	−0.3 (4.2)	−0.2 (2.0)	0.9 (2.7)
MPAP	16.6 (9.5)	−0.7 (13.8)	4.3 (11.0)	1.0 (1.8)
RAP	2.3 (2.3)	101 (259)§	71 (167)	18 (27)
RV d*P*/d*t*max	586 (110)	−21.8 (12.8)§	−11.0 (13.5)	−0.2 (6.5)
PBF	1.46 (0.46)	−5.8 (21.1)	−2.2 (14.6)	9.2 (8.0)
RVSV	11.3 (3.2)	−12.6 (5.5)†§	−5.6 (4.3)‡	3.9 (4.9)
Anaemia group (*n*=8)				
MAP	84 (13)	−11.1 (5.6)§	4.1 (4.1)	1.3 (1.8)
HR	122 (13)	4.0 (6.0)	2.9 (3.7)	2.3 (2.3)
MPAP	12.9 (3.7)	1.8 (5.9)	4.5 (4.0)§	0.8 (6.8)
RAP	1.3 (1.5)	150 (190)§	96 (128)§	16 (26)
RV d*P*/d*t*max	535 (88)	−16.9 (10.0)§	−7.0 (9.2)	1.1 (5.1)
PBF	1.72 (0.32)	8.7 (8.3)	7.4 (7.1)§	9.2 (5.1)§
RVSV	14.2 (3.1)	4.6 (6.5)	4.4 (6.4)	6.9 (5.9)§
Anaemia acidosis group (*n*=7)				
MAP	85 (10)	−6.7 (7.9)	7.8 (10.3)	5.6 (6.4)
HR	121 (15)	1.1 (3.9)	−0.8 (2.6)	0.8 (0.9)
MPAP	15.4 (3.4)	−0.4 (7.1)	4.3 (10.0)	1.9 (3.7)
RAP	2.3 (1.5)	66 (79)§	47 (47)§	0 (14)
RV d*P*/d*t*max	609 (158)	−10.5 (7.8)	−2.8 (9.2)	1.0 (9.2)
PBF	1.91 (0.38)‡	−1.0 (12.1)	−2.0 (9.0)	4.8 (5.5)
RVSV	16.1 (3.6)*	−3.3 (4.7)	−1.2 (5.0)	4.1 (6.2)

cant decreases in MAP and RV d*P*/d*t*max occurred in all groups except for the anaemia acidosis group. In the non-acidosis groups (the control and anaemia groups), PBF and RVSV increased significantly from baseline values at the end of the observation period. PBF and RVSV values in the metabolic acidosis group decreased significantly for a period of 1 min after administration of sodium bicarbonate. The percentage reduction in RVSV in the metabolic acidosis group at 30 s after administration of bicarbonate was significantly more than in the three other groups ($P<0.05$, table 2). HR was unchanged after administration of sodium bicarbonate in all groups. The mean times at which maximum changes in MAP, RV d*P*/d*t*max and PBF occurred were all within 20 s of bicarbonate administration: MAP: 18 (7), 19 (11), 17 (4), 13 (4) s; RV d*P*/d*t*max: 16 (2), 20 (4), 14 (3), 16 (4) s; PBF: 17 (3), 20 (6), 15 (6), 17 (6) s in the control, metabolic acidosis, anaemia and anaemia acidosis groups, respectively.

Discussion

We have observed cardiodepressant effects associated with rapid administration of sodium bicarbonate 1 mmol kg^{-1} in control, metabolic acidosis and anaemia groups, demonstrated by significant depression of RV d*P*/d*t*max, and this response was attenuated in the anaemia acidosis group. It is not explained simply by dilution, as depression of RV d*P*/d*t*max was also observed in the anaemia group. Maximum reductions in RV d*P*/d*t*max, PBF and MAP occurred within 20 s of administration of bicarbonate, but the changes were transient. Although the extent and duration of these changes may not be clinically important, they may be significant in patients undergoing cardiopulmonary bypass where normovolaemic haemodilution is practised, and also after massive bleeding and haemodilution complicated by metabolic acidosis.

The cardiodepressant effect of bicarbonate is considered to be caused by a rapid decrease in the intracellular pH of the myocardium caused by free diffusion of carbon dioxide liberated from bicarbonate[2], rather than a result of volume expansion[13]. The fact that such a detrimental effect of bicarbonate is more pronounced during metabolic acidosis suggests that a further reduction in intramyocardial pH occurs with pre-existing extracellular acidosis at pHa 7.2. A marginally reduced intracellular pH is not cardiodepressant in itself, as evidenced by comparable haemodynamic variables between the control and metabolic acidosis groups in our study and previous experiments[14–16].

It is not clear from our study why the haemodynamic response to sodium bicarbonate was more pronounced during metabolic acidosis but less marked when there was coexisting normovolaemic haemodilution. Clinical[8 9] and experimental[10–12] studies have observed typical responses to normovolaemic haemodilution characterized by an increase in stroke volume and cardiac index, and a decrease in systemic vascular resistance, with essentially no changes in arterial pressure and HR. One possible explanation is that these underlying haemodynamic changes induced by haemodilution may have counteracted the cardiodepressant effect of bicarbonate.

There are three possible shortcomings to our study. First, this was not a dose–response study, and interpretation of the results should be confined to the doses studied. Most importantly, bicarbonate was given over a brief period of time. A smaller dose of bicarbonate or slower speed of injection could have resulted in less depression of the myocardium[4]. The dose of bicarbonate in our study has been used in previous studies and is recommended in some circumstances during cardiopulmonary resuscitation[4 17 18]. In addition, the degree of metabolic acidosis studied would not be expected to produce significant cardiovascular depression[14–16]. With more profound acidosis where myocardial depression caused by acidosis *per se* is apparent, cardiac depression induced by bolus administration of bicarbonate may be more aggravated. Second, we did not determine circulating blood volume. In previous experiments, a ratio of 1:2.5 of bleeding and exchange crystalloid infusion resulted in a constant blood volume estimated by ^{125}I-labelled albumin in dogs[11]. In contrast, exchange transfusion with a ratio of 1:3 has been reported to produce progressive metabolic acidosis, hypovolaemia and eventually death[19]. These previous conflicting results may be attributed in part to the differences in time for equilibration. Our study has confirmed that an equilibration period of at least 2 h is required after surgical preparation, establishment of acidosis or haemodilution, during which lactated Ringer's solution was infused continuously. A significant amount of extravasation of plasma, had it occurred during this period, must have been replaced, as indicated by the unchanged PAOP before and after haemodilution, before administratin of bicarbonate in the anaemia and anaemia acidosis groups.Third, administration of hydrochloric acid effectively induced extracellular acidosis, but we did not measure intracellular pH. However, greater depression of cardiac performance with administration of bicarbonate in the metabolic acidosis group than in the control group suggests marginally disturbed intracellular environment by maintenance of extracellular pH at 7.2 for 2 h or longer. In an *in vivo* experiment using rabbits, i.v. infusion of hydrochloric acid followed by an equilibration period of 1 h produced dose-dependent linear decreases in intracellular pH of the left ventricular myocardium[20].

References

1. Arieff AI. Indications for use of bicarbonate in patients with metabolic acidosis. *British Journal of Anaesthesia* 1991; **67**: 165–177.
2. Planta M, Weil MH, Gazmuri RJ, Bisera J, Rackow EC. Myocardial acidosis associated with CO_2 production during cardiac arrest and resuscitation. *Circulation* 1989; **80**: 684–692.
3. Clancy RL, Cingolani HE, Taylor RR, Graham TP, Gilmore JP. Influence of sodium bicarbonate on myocardial performance. *American Journal of Physiology* 1967; **212**: 917–923.
4. Huseby JS, Gumprecht DG. Hemodynamic effect of rapid bolus hypertonic sodium bicarbonate. *Chest* 1981; **79**: 552–554.
5. Graf H, Leach W, Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science* 1985; **227**: 754–756.
6. Bersin RM, Chatterjee K, Arieff AI. Metabolic and hemodynamic consequences of sodium bicarbonate administration in patients with heart disease. *American Journal of Medicine* 1989; **87**: 7–14.
7. Tanaka M, Nishikawa T. Acute hemodynamic changes by sodium bicarbonate in respiratory or metabolic acidosis in dogs. *Anesthesiology* 1994; **81**: A716.
8. Mouren S, Baron JF, Hag B, Arthaud M, Viars P. Normovolemic hemodilution and lumbar extradural anesthesia. *Anesthesia and Analgesia* 1989; **69**: 174–179.
9. Catoire P, Saada M, Liu N, Delaunay L, Rauss A, Bonnet F. Effect of preoperative normovolemic hemodilution on left ventricular segmental wall motion during abdominal aortic surgery. *Anesthesia and Analgesia* 1992; **75**: 654–659.
10. Estafanous FG, Smith CE, Selim WM, Tarazi RC. Cardiovascular effects of acute normovolemic hemodilution in rats with disopyramide-induced myocardial depression. *Basic Research of Cardiology* 1990; **85**: 227–236.
11. Geha AS. Coronary and cardiovascular dynamics and oxygen availability during acute normovolemic anemia. *Surgery* 1976; **80**: 47–53.

12. Wilkerson DK, Rosen AL, Sehgal LR, Gould SA, Sehgal HL, Moss GS. Limits of cardiac compensation in anemic baboons. *Surgery* 1988; **103**: 665–670.
13. Nishikawa T. Acute haemodynamic effects of sodium bicarbonate in canine respiratory or metabolic acidosis. *British Journal of Anaesthesia* 1993; **70**: 196–200.
14. Downing SE, Talner NS, Gardner TH. Cardiovascular responses to metabolic acidosis. *American Journal of Physiology* 1965; **208**: 237–242.
15. Wildenthal K, Mierzwiak DS, Myers RW, Mitchell JH. Effects of acute lactic acidosis on left ventricular performance. *American Journal of Physiology* 1968; **214**: 1352–1359.
16. Andersen MN, Border JR, Mouritzen CV. Acidosis, catecholamines and cardiovascular dynamics: when does acidosis require correction? *Annals of Surgery* 1967; **166**: 344–356.
17. Standards and guidelines for cardiopulmonary resuscitation and emergency cardiac care. *Journal of the American Medical Association* 1986; **255**: 2942.
18. Guerci AD, Chandra N, Johnson E, Rayburn B, Wurmb E, Tsitlik J, Halperin HR, Siu C, Weisfeldt ML. Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. *Circulation* 1986; 74 (Suppl. IV): 75–79.
19. Cervera AL, Moss G. Progressive hypovolemia leading to shock after continuous hemorrhage and 3:1 crystalloid replacement. *American Journal of Surgery* 1975; **129**: 670–674.
20. Poole-Wilson PA, Cameron IR. Intracellular pH and K of cardiac and skeletal muscle in acidosis and alkalosis. *American Journal of Physiology* 1975; **229**: 1305–1310.

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Inhalation of a nitric oxide synthase inhibitor to a hypoxic or collapsed lung lobe in anaesthetized pigs: effects on pulmonary blood flow distribution

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Summary

I.v. administration of the nitric oxide synthase inhibitor, nitro-L-arginine methyl ester (L-NAME), not only reduces blood flow in a hypoxic lung region but also causes systemic vasoconstriction and a decrease in cardiac output. In this study, we delivered nebulized L-NAME 0.2–1 mg kg^{-1} to the left lower lobe of 10 anaesthetized pigs. The left lower lobe was made hypoxic by selective inhalation of 5% oxygen or collapsed by interrupted ventilation, or both. Inhalation of L-NAME reduced fractional blood flow to the left lower lobe from 5.3 (SD 3.1)% to 1.7 (1.4)% ($P<0.05$) in lobar hypoxia and from 6.0 (3.3) to 2.7 (2.7)% ($P<0.05$) in lobar collapse. These reductions were accompanied by a significant increase in Pa_{O_2}. There were no significant changes in arterial pressure, cardiac output or heart rate. We have shown that selective inhalation of L-NAME reduced blood flow to a hypoxic or collapsed lung region without systemic effects. The possible role for nitric oxide synthase inhibition in reducing shunt during one-lung ventilation, however, requires further study. (*Br. J. Anaesth.* 1996;**77**:413–418)

Key words

Pharmacology, nitric oxide. Ventilation, one-lung. Lung, blood flow. Pig.

In 1980, Furchgott and Zawadski[1] reported that vasodilatation caused by acetylcholine was endothelium-dependent and that endothelial cells, when stimulated, can release substances that cause relaxation of vascular smooth muscle. One substance has been identified as nitric oxide[2 3].

There is now evidence that nitric oxide is produced in the lung and is important in the regulation of the tone of the pulmonary vessels. Endogenous nitric oxide production has been demonstrated by Gustafsson and colleagues[4] who measured nitric oxide in the exhaled breath of rabbits and humans. When the rabbit was hypoxaemic, the exhaled nitric oxide concentration decreased. Nitric oxide synthase, constitutive and inducible, has been found in many cell types in human lung tissue[5].

Inhaled nitric oxide at concentrations of 5–80 ppm has been shown to diminish or abolish the hypoxic vasoconstrictor response and pulmonary hypertension caused by thromboxane analogues in conscious lambs[6 7] and in a porcine model of adult respiratory distress syndrome (ARDS)[8]. Inhalation of nitric oxide may reduce pulmonary hypertension in healthy volunteers breathing hypoxic gas[9] and in patients with ARDS[10].

When endogenous nitric oxide production was blocked by administration of L-arginine analogues, anaesthetized rabbits developed hypoxaemia and an increase in respiratory frequency[11]. There was also an increase in pulmonary vascular resistance, which was more marked during hypoxia than during normoxia. In regional lung hypoxia, blockage of endogenous nitric oxide production caused a shift of blood away from the hypoxic region and improved arterial oxygenation[12 13]. By inhaling nitric oxide to the non-hypoxic region, this blood shift was more accentuated and blood flow to the hypoxic region was almost abolished[13]. These findings indicate that administration of nitric oxide inhibits hypoxic pulmonary vasoconstriction and that blockage of endogenous nitric oxide production enhances it. The combination of inhaled nitric oxide and nitric oxide synthase inhibitors provides a method of altering pulmonary blood flow distribution that may be of clinical use in acute lung injury and in one-lung ventilation. However, i.v. administration of nitric oxide synthase inhibitors causes systemic effects with increased systemic arterial pressure and lowered cardiac output[13].

In this study, we have examined the hypothesis that *inhalation* of a nitric oxide synthase inhibitor, nitro-L-arginine methyl ester (L-NAME), to a hypoxic lung region would decrease blood flow to this region without causing systemic effects. The study was performed in an animal model where hypoxia was induced in the left lower lobe. To simulate one-lung ventilation we also studied the effect of inhaled L-NAME to a subsequently collapsed left lower lobe.

Materials and methods

The study was approved by the Animal Research Ethics Committee of Uppsala University. Twelve pigs of Swedish country breed, weighing 25–32 kg, were used in the study. The animals were premedicated with pentobarbitone 20 mg kg^{-1} and atropine 0.5 mg i.p. Anaesthesia was induced 30 min later with pentobarbitone 180–360 mg i.v. and maintained with a continuous infusion of chlormethiazole 800–1600 mg h^{-1} [14] and pancuronium 4–8 mg h^{-1}. Repeated

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doses of fentanyl 0.2–0.5 mg i.v. were given as necessary. After induction, the animals were placed in the supine position for the remainder of the study. Isotonic saline 10–15 ml kg^{-1} h^{-1} was given for hydration.

VENTILATION

A tracheotomy was performed after induction of anaesthesia and two cuffed tracheal tubes were inserted. One tube with an internal diameter of 6.0 mm was positioned in the trachea and the second, with an internal diameter of 4.5 mm, was placed in the bronchus of the left lower lobe. In this way, the left lower lobe could be isolated and ventilated independently, a technique described in detail in a previous report[13]. Two synchronized, volume-controlled ventilators (Siemens Servo ventilator 900 C, Siemens Elema, Lund, Sweden) were used and 30% of the total minute ventilation was administered to the left lower lobe. This volume corresponded to the weight of the left lower lobe as a percentage of the total weight of both lungs (unpublished data, Fredén and colleagues, 1993). Both ventilators were adjusted to give a positive end-expiratory pressure (PEEP) of +5 cm H_2O and the inspired oxygen fraction (F_{IO_2}) was set at 0.8. The oxygen cell of the ventilator was used to measure F_{IO_2}. Ventilatory frequency was maintained at 20 bpm and tidal volume was adjusted to obtain a Pa_{CO_2} of 5.2–6.2 kPa. To prevent atelectasis, the lungs were ventilated three times with a double tidal volume at the beginning of each measurement period (see experimental design).

PREPARATION

An ear vein was cannulated for induction and maintenance of anaesthesia. A triple-lumen, balloon-tipped catheter (Swan Ganz No. 7-French gauge) was introduced via the right external jugular vein to the pulmonary artery for blood sampling and pressure recording. A large bore catheter was inserted into the contralateral jugular vein for infusion purposes with its tip in the superior caval vein. The right carotid artery was cannulated to measure arterial pressure and sample blood.

Via a median sternotomy, the artery to the left lower lobe and the pulmonary artery were identified, ultrasonic flow probes were attached and connected to a flowmeter (probes, 6 SB and 12 SB; flowmeter, T208; Transonic, Ithaca, NY, USA).

MEASUREMENTS

Arterial, central venous and pulmonary artery catheters were attached to appropriate pressure transducers (Sorenson Transpac transducers, Abbott Critical Care Systems, IL, USA). Mean arterial pressure, mean pulmonary arterial pressure, central venous pressure and pulmonary capillary wedge pressure were recorded on a Marquette 7010 monitor (Marquette Electronics Inc., WI, USA). Pressures were averaged over the whole respiratory cycle and the mid-thorax was used as the zero reference level.

Mixed venous and arterial blood samples were collected for blood-gas analysis (ABL 3, Radiometer, Copenhagen, Denmark), oxygen saturation and haemoglobin concentration (OSM 3, Radiometer, Copenhagen, Denmark). Cardiac output and blood flow to the left lower lobe were measured continuously with the flow probes.

Mean airway pressure and expired minute volume were recorded from both ventilators.

EXPERIMENTAL DESIGN

After preparation, a rest period of 30 min was allowed before baseline measurements were obtained. Each set of measurements comprised mean arterial pressure, mean pulmonary artery pressure, heart rate, central venous pressure, pulmonary capillary wedge pressure, cardiac output, blood flow to the left lower lobe, arterial and mixed venous blood-gas tensions, saturations and airway pressures. F_{IO_2} was maintained at 0.8 in the right lung and the upper and middle lobes of the left lung. Three different settings were used for the left lower lobe: baseline and control (F_{IO_2} 0.8), lobar hypoxia (5% oxygen, 5% carbon dioxide and 90% nitrogen (AGA, Lidingo, Sweden)) and lobar collapse (with the ventilator to the left lower lobe disconnected). Thirty minutes were allowed at each setting before measurements were made.

L-NAME (Sigma Chemical Co, St Louis, MO, USA) was dissolved in isotonic saline 20 ml and delivered to the left lower lobe with an ultrasonic nebulizer (De Vilbiss, Ultraneb 99, PA, USA). Inhalation of L-NAME was always performed during lobar hypoxia as preliminary experiments had shown that inhalation during normoxia caused systemic effects, presumably because of increased absorption of L-NAME caused by larger lobar blood flow.

The different experiments used in the study are outlined in table 1. In four animals, the effect of inhaled L-NAME was tested during both lobar hypoxia and lobar collapse. To ensure that a preceding period of lobar hypoxia did not interfere with any effects of lobar collapse on blood flow or vice versa, three animals were investigated with lobar collapse only and three with lobar hypoxia only. Evaluation of these different designs showed no differences in the response to lobar hypoxia or collapse and therefore the results are given for the two groups: lobar hypoxia (n=7) and lobar collapse (n=7).

Re-opening of the left lower lobe after lobar collapse was controlled in two ways. Via the thoracotomy, the lobe was examined visually to ensure that no parts of the lobe were atelectatic and, before inhalation of L-NAME, fractional blood flow to the left lower in the control situation was compared with the baseline recording.

In three of the animals with lobar collapse, a third period of lobar collapse was induced, measurements were performed and followed by i.v. injection of L-arginine 1 g kg^{-1} (Sigma Chemical Co, St Louis, MO, USA) to reverse the effect of L-NAME, and new recordings were performed.

In two additional animals, L-NAME 0.2 mg kg^{-1} was delivered to both lungs and systemic and pulmonary haemodynamic measurements, and arterial and mixed venous blood-gas tensions were measured during normoxia and hypoxia (F_{IO_2} 0.12) before and after inhalation. Cardiac output was measured with thermodilution as no thoracotomy was performed, 10 ml of isotonic saline at room temperature were injected as a bolus and cardiac output was computed

Table 1 A survey of the three different experimental designs used in the study showing F_{IO_2} to the right lung and upper and middle lobes of the left lung (F_{IO_2} RL), and F_{IO_2} to the left lower lobe (F_{IO_2} LLL); "X" marks the different steps in each experiment. Experiment I included four animals and experiments II and III three each. Experiments I and II were used for the "lobar hypoxia" group (n=7) and experiments II and III for the "lobar collapse" group (n=7) (see tables 2 and 3)

	Baseline	Lobar collapse	Control	Lobar hypoxia	Inhalation L-NAME	Lobar hypoxia	Control	Lobar collapse	Control
F_{IO_2} RL	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
F_{IO_2} LLL	0.8	Non-vent.	0.8	0.05	0.05	0.05	0.8	Non-vent.	0.8
Experiment I (n=4)	X	X	X	X	X	X	X	X	X
Experiment II (n=3)	X			X	X	X	X		
Experiment III (n=3)	X	X	X		X		X	X	X

Table 2 Lobar perfusion and arterial oxygenation in the two groups given lobar inhalation of L-NAME (mean (SD)). Fractional blood flow to the left lower lobe (Q_{LLL}/Q_T) and arterial oxygenation at baseline (F_{IO_2} 0.8), during lobar hypoxia-collapse before and after L-NAME, and in the control situation (F_{IO_2} 0.8). Ten animals were used for these two groups; of these, four were studied during both lobar hypoxia and lobar collapse, hence n=7 in both groups (also see table 1). Wilcoxon signed rank test was performed to compare baseline with control ($^*P < 0.05$) and to compare conditions during lobar hypoxia–collapse before and after L-NAME ($^\dagger P < 0.05$)

	Lobar hypoxia				Lobar collapse			
	Baseline	Before L-NAME	After L-NAME	Control	Baseline	Before L-NAME	After L-NAME	Control
Q_{LLL}/Q_T (%)	23.2 (5.5)	5.3 (3.1)	1.7 (1.4)†	18.8 (4.5)*	21.2 (6.5)	6.0 (3.3)	2.7 (2.7)†	19.2 (4.0)
Pa_{O_2} (kPa)	38.9 (8.5)	23.3 (6.7)	28.8 (9.2)†	36 (4.6)	37.5 (9.9)	21.6 (4.7)	24.8 (6.0)†	33.9 (8.7)

(cardiac output computer Marquette 7010, Marquette Electronics Inc., WI, USA). Three injections were given for each measurement and the mean calculated. The injections were distributed evenly over the respiratory cycle.

When the experiment was completed the animal was killed with an i.v. injection of potassium chloride and the lungs were removed for inspection.

Fractional blood flow to the left lower lobe was calculated as blood flow to the left lower lobe divided by cardiac output. Pulmonary vascular resistance (PVR) was calculated using standard formulae.

STATISTICS

All data are given as mean (SD). Two paired comparisons were performed: between baseline data before inhalation and control data after inhalation of L-NAME; and between lobar hypoxia–collapse data before and after inhalation of L-NAME. Wilcoxon's signed rank test was used and P<0.05 was considered significant.

Results

Table 2 shows fractional blood flow to the left lower lobe and arterial oxygenation for the two groups with lobar hypoxia and lobar collapse, and table 3 shows other essential data for the two groups. The following recordings are presented: baseline, hypoxia–collapse preceding administration of L-NAME, hypoxia–

Table 3 Inhalation of L-NAME during lobar hypoxia and lobar collapse (mean (SD)). Data shown are baseline (F_{IO_2} 0.8) before lobar hypoxia–collapse, during lobar hypoxia–collapse before and after inhalation of L-NAME, and in the control situation (F_{IO_2} 0.8) after inhalation of L-NAME. Ten animals were used for these two groups; of these, four were studied during both lobar hypoxia and lobar collapse, hence n=7 in both groups (also see table 1). Cardiac output (Q_T), arterial carbon dioxide tension (Pa_{CO_2}), mean arterial pressure (MAP), heart rate (HR), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), mixed venous oxygen tension ($P\bar{v}_{O_2}$) and pulmonary vascular resistance (PVR) are shown. Wilcoxon signed rank test was performed to compare baseline with control in the two groups ($^*P < 0.5$) and to compare conditions during lobar hypoxia–collapse before and after inhalation of L-NAME ($^\dagger P < 0.05$)

	Lobar hypoxia				Lobar collapse			
	Baseline	Before L-NAME	After L-NAME	Control	Baseline	Before L-NAME	After L-NAME	Control
Q_T (litre min^{-1})	2.9 (0.6)	3.1 (0.7)	2.8 (0.5)	2.7 (0.6)	3.1 (0.7)	3.2 (0.7)	3.0 (0.5)	2.8 (0.4)
Pa_{CO_2} (kPa)	5.44 (0.9)	6.07 (0.8)	6.21 (0.5)	5.27 (0.6)	5.6 (0.6)	6.0 (0.3)	6.2 (0.4)	5.8 (0.5)
MAP (mm Hg)	84 (11)	87 (14)	87 (17)	90 (12)	80 (7)	83 (10)	88 (9)	85 (6)
HR (beat min^{-1})	118 (18)	130 (21)	139 (26)	132 (30)	116 (16)	121 (16)	136 (20)	130 (7)
MPAP (mm Hg)	18 (3)	23 (4)	25 (4)†	22 (3)*	17 (2)	20 (5)	23 (2)	21 (3)*
PCWP (mm Hg)	7 (1.4)	8 (1.6)	9 (1.6)	9 (2.2)*	7 (0.9)	8 (2.8)	8 (1.9)	8 (1.1)
CVP (mm Hg)	6 (2.7)	7 (2.5)	7 (2.4)	8 (3.1)	6 (2.7)	7 (3.1)	6 (1.8)	6 (1.7)
$P\bar{v}_{O_2}$ (kPa)	5.9 (0.5)	5.9 (0.4)	6.1 (0.8)	5.8 (0.5)	5.9 (0.4)	5.8 (0.3)	5.8 (0.5)	6.0 (0.4)
PVR (dyn s cm^{-5})	303 (47)	383 (104)	449 (136)†	425 (118)	276 (57)	309 (101)	401 (85)†	389 (83)*

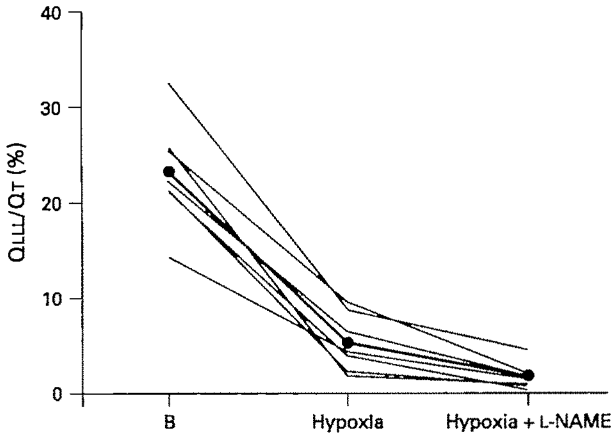

Figure 1 Relative perfusion (*QLLL/QT*) to the left lower lobe at baseline (B) and during lobar hypoxia, before (Hypoxia) and after (Hypoxia+L-NAME) inhalation of L-NAME 0.2–1 mg kg^{-1}. Individual and mean values (bold line) are shown. The marked decrease in lobar perfusion by hypoxia was enhanced significantly by inhalation of L-NAME.

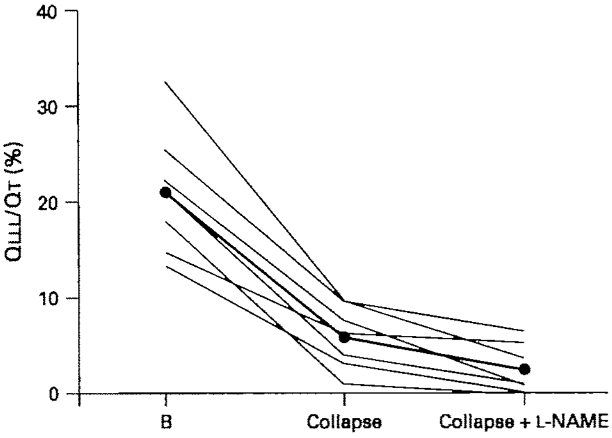

Figure 2 Relative perfusion (*QLLL/QT*) to the left lower lobe at baseline (B) and during lobar collapse, before (Collapse) and after (Collapse+L-NAME) inhalation of L-NAME 0.2–1 mg kg^{-1}. Individual and mean values (bold line) are shown. The marked decrease in lobar perfusion caused by lobar collapse was enhanced significantly by inhalation of L-NAME.

pcollapse subsequent to L-NAME and the last control recording.

BASELINE

At baseline, cardiac output, mean arterial pressure, mean pulmonary arterial pressure, central venous pressure and pulmonary capillary wedge pressure values were similar to those reported previously for pigs undergoing mechanical ventilation with healthy lungs[15]. Fractional blood flow to the left lower lobe was 23.2 (5.5)% in the hypoxic group and 21.1 (6.5)% in the lobar collapse group, which is in accordance with previous reports[13]. Arterial oxygenation was good with Pa_{O_2} values of 38.9 (8.5) kPa and 37.5 (9.9) kPa, respectively. Both groups were normocapnic. During the course of the experiment, mean airway pressure in the left lower lobe varied from 8.7 (0.5) to 9.9 (0.2) cm H_2O and, in the right lung and upper and middle lobes of the left lung, 9.9 (0.4) to 10.4 (0.2) cm H_2O; these changes were not significant (data not shown in tables).

LOBAR HYPOXIA AND L-NAME

Hypoxia of the left lower lobe caused a marked reduction in fractional blood flow to the left lower lobe to 5.3 (3.1) % and a decrease in Pa_{O2}. Mean pulmonary arterial pressure increased by a mean of 5 mm Hg. Delivery of L-NAME to the hypoxic left lower lobe caused a further reduction in fractional blood flow to the left lower lobe to 1.7 (1.4) % ($P<0.05$) (see fig. 1) and a significant increase in Pa_{O_2}. There were no significant changes in cardiac output, heart rate or mean arterial pressure. There was a further increase in mean pulmonary arterial pressure. When the left lower lobe again received hyperoxic gas (FI_{O_2} 0.8), after inhalation of L-NAME, a persistent decrease in lobar perfusion and increase in mean pulmonary arterial pressure were seen compared with baseline measurements, whereas Pa_{O_2} did not differ significantly from baseline.

LOBAR COLLAPSE AND L-NAME

Collapse of the left lower lobe caused a reduction in fractional blood flow to the left lower lobe to 6.0 (3.3) % and a decrease in Pa_{O_2}. There was also an increase in mean pulmonary arterial pressure by a mean of 3 mm Hg. Re-opening of the lobe (FI_{O_2} 0.8) before L-NAME increased fractional blood flow to the left lower lobe to 19.4 (4.0) % and Pa_{O_2} to 35.8 (6.3) kPa. These values did not differ significantly from baseline (data not shown in tables).

When the left lower lobe was collapsed a second time, after inhalation of L-NAME, fractional blood flow to the left lower lobe decreased to 2.7 (2.7) % ($P<0.05$) (fig. 2) and Pa_{O_2} increased significantly. There was a small, non-significant increase in mean pulmonary arterial pressure. There were no significant changes in cardiac output, heart rate or mean arterial pressure. When the left lower lobe at the end of the experiment was ventilated with 80% oxygen, fractional blood flow to the left lower lobe and Pa_{O_2} did not differ significantly from baseline measurements, but mean pulmonary arterial pressure remained increased.

L-ARGININE

I.v. injection of L-arginine 1 mg kg^{-1} to three animals reversed the reduction in fractional blood flow to the left lower lobe caused by inhaled L-NAME. In these pigs with lobar collapse, mean fractional blood flow to the left lower lobe was 9.1% before L-NAME and 3.9% after, while injection of L-arginine increased it to 8.7 % (fig. 3).

L-NAME TO BOTH LUNGS

After delivery of L-NAME to both lungs in two animals, there was an increase in mean arterial pressure of approximately 20 mm Hg both during normoxia and hypoxia. There was also an increase in mean pulmonary arterial pressure (3 mm Hg during normoxia and 4–5 mm Hg during hypoxia), but there was no change in cardiac output or arterial oxygenation.

Discussion

The major finding of this study was that selective inhalation of a nitric oxide synthase inhibitor to an hypoxic or subsequently collapsed lobe reduced

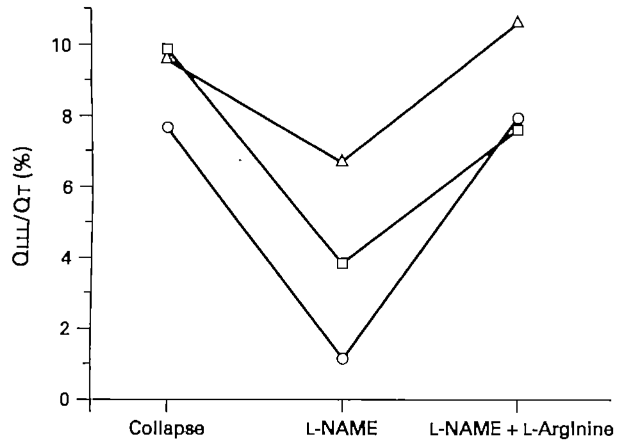

Figure 3 In three pigs with lobar collapse, L-arginine 1 g kg^{-1} was infused after inhalation of L-NAME; relative perfusion (*Q*LLL/*Q*T) of the collapsed lobe before inhalation of L-NAME (Collapse), after inhalation of L-NAME (L-NAME) and after infusion of L-arginine (L-NAME+L-Arginine). L-Arginine reversed the effect of L-NAME in all three animals.

blood flow to this lobe and improved arterial oxygenation without causing systemic effects. It has been reported previously that nitric oxide synthase inhibitors constrict pulmonary vessels and that this effect is more pronounced during hypoxic conditions[11]. In regional hypoxia, i.v. administration of nitric oxide synthase inhibitors enhances hypoxic pulmonary vasoconstriction and thus diverts blood flow away from the hypoxic region and improves arterial oxygenation[12 13]. However, i.v. administration of L-NAME causes an increase in mean arterial pressure and a decrease in cardiac output, except when used in very small doses [12 13].

Administration of L-NAME via the airways to the target organ, that is the hypoxic lobe, caused a reduction in lobar blood flow similar to that seen during i.v. infusion[13]. A much lower dose was delivered by nebulization than by infusion (0.2–1 mg kg^{-1} *vs* 30 mg kg^{-1}); however, no dose–response experiments were performed in either study. In this way, systemic effects could also be avoided and neither cardiac output nor mean arterial pressure changed. In addition, inhalation of L-NAME caused only a small increase in mean pulmonary arterial pressure by approximately 2–3 mm Hg, which can be compared with the pronounced increase seen after i.v. administration, when mean pulmonary arterial pressure increased by more than 15 mm Hg[13]. Delivery of L-NAME to both lungs in two animals, caused systemic effects with a pronounced increase in mean arterial pressure, presumably because of higher uptake of L-NAME to the systemic circulation.

Inhalation of nitric oxide synthase inhibitors, L-NAME and N^{G}-monomethyl-L-arginine (L-NMMA), has been shown previously to cause an increase in tracheal tone and also to induce airway hyper-responsiveness to histamine, carbachol and metacholine[16]. In this study, mean airway pressure did not change during or after inhalation of L-NAME but this does not preclude smaller alterations in airway tone.

In regional hypoxia, the hypoxic vasoconstrictor response has been reported to be complete after 15 min of hypoxia; prolonged hypoxia does not appear to potentiate or decrease this response[17 18] although one study reported differently[19]. Our measurements were performed after 30 min of hypoxia, at a time when the vasoconstrictor response was assumed to be stable. In atelectasis, the vascular response is of similar magnitude, but Glasser and colleagues reported it to be slower, with a maximal response after 60 min[20]. Our recordings were made after 30 min of lobar collapse, which according to Glasser and colleagues is too early, however, we found that lobar blood flow was always stable after 15–20 min of lobar collapse.

Repeated hypoxic challenges have been reported to potentiate the hypoxic vasoconstrictor response in lobar hypoxia in the dog[21] which, in our study, could be a cause of error. However, there are also reports showing no potentiation of hypoxic pulmonary vasoconstriction in dogs with unilateral hypoxia[22] or in humans[23]. To our knowledge, there are no reports of repeated regional hypoxia induced in pigs but unpublished data from our laboratory showed no enhancement of the hypoxic response after three periods of lobar hypoxia, each lasting for 30 min (Fredén and colleagues, 1995).

In the ventilated lung, alveolar oxygen is the most important determinant of hypoxic pulmonary vasoconstriction but, in atelectasis, $P\bar{v}_{O_2}$ becomes more important[24]. A reduction in $P\bar{v}_{O_2}$ could therefore decrease fractional blood flow to the left lower lobe and be a source of error; however $P\bar{v}_{O_2}$ did not alter in any of the groups in our study (see table 3).

The clinical implication of this study is one-lung ventilation in thoracic surgery. Inhalation of L-NAME to the lung that is not to be ventilated would, according to our results, decrease shunting and improve arterial oxygenation. Improvement in Pa_{O_2} in this study was not impressive but it is important to keep in mind that the pig is known to develop a very strong vascular response to hypoxia[25], and blood flow to the left lower lobe was reduced markedly during hypoxia or the collapse *per se* (see table 2). Furthermore, the effect of L-NAME may have been more marked if one entire lung had been rendered hypoxic rather than just one lobe. The use of one lobe instead of one lung in this study was because of the bronchial anatomy of the pig, which makes separation of the two lungs difficult. However, increased absorption of L-NAME to the circulation and ensuing systemic effects cannot be excluded if L-NAME is delivered to a whole lung.

In ARDS, inhalation of nitric oxide has been shown to improve oxygenation and lower pulmonary artery pressures[10]. A combination of inhaled nitric oxide and i.v. administration of a nitric oxide synthase inhibitor has been tested in animal models of ARDS[26 27]. Although the results have varied, it appears to be an interesting approach to constrict vessels in shunt areas. Obviously our model based on inhalation of L-NAME would not be feasible in ARDS; it might even be harmful, as L-NAME would only reach the ventilated areas and probably increase the degree of shunting.

In conclusion, the present study has shown that the selective delivery of nebulized L-NAME reduces blood flow to a hypoxic or collapsed lung lobe without causing any systemic effects. It may, in the future, be a way of reducing shunting during one lung ventilation; this, however, requires further study.

Acknowledgements

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References

1. Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature (London)* 1980; **288**: 373–376.
2. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature (London)* 1987; **327**: 524–526.
3. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proceedings of the National Academy of Sciences USA* 1987; **84**: 9265–9269.
4. Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochemical and Biophysical Research Communications* 1991; **181**: 852–857.
5. Kobzik L, Bredt DS, Lowenstein CJ, Drazen J. Gaston B. Sugarbaker D, Stamler JS. Nitric oxide synthase in the human and rat lung: immunocytochemical and histochemical localization. *American Journal of Respiratory Cell and Molecular Biology* 1993; **9**: 371–377.
6. Frostell CG, Fratacci M-D, Wain JC, Jones R. Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991; **83**: 2038–2047.
7. Fratacci M-D, Frostell CG, Chen T-Y, Wain JC, Robinson DR, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator of heparin–protamine vasoconstriction in sheep. *Anesthesiology* 1991; **75**: 990–999.
8. Weitzberg E, Rudehill A, Alving K, Lundberg JM. Nitric oxide inhalation selectively attenuates pulmonary hypertension and arterial hypoxia in porcine endotoxin shock. *Acta Physiologica Scandinavica* 1991; **143**: 451–452.
9. Frostell CG, Blomqvist H, Hedenstierna G, Lundberg JM, Zapol WM. Inhaled nitric oxide selectively reverses human pulmonary vasoconstriction without causing systemic vasodilation. *Anesthesiology* 1993; **78**: 427–435.
10. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328**: 399–405.
11. Persson MG, Gustafsson LE, Wiklund NP, Moncada S, Hedqvist P. Endogenous nitric oxide as a probable modulator of pulmonary circulation and hypoxic pressor response *in vivo*. *Acta Physiologica Scandinavica* 1990; **140**: 449–457.
12. Sprague RS, Thiemermann C, Vane JR. Endogenous endothelium-derived relaxing factor opposes hypoxic pulmonary vasoconstriction and supports blood flow to hypoxic alveoli in anesthetized rabbits. *Proceedings of the National Academy of Sciences USA* 1992; **89**: 8711–8715.
13. Freden F, Wei SZ, Berglund JE, Frostell C, Hedenstierna G. Nitric oxide modulation of pulmonary blood flow distribution in lobar hypoxia. *Anesthesiology* 1995; **82**: 1216–1225.
14. Christensen JH, Andreasen F, Kristoffersen MB. Comparison of the anaesthetic and haemodynamic effects of chlormetiazol and thiopentone. *British Journal of Anaesthesia* 1983; **55**: 391–397.
15. Freden F, Cigarini I, Mannting F, Hagberg A, Lemaire F, Hedenstierna G. Dependence of shunt on cardiac output in unilobar oleic acid edema. *Intensive Care Medicine* 1993; **19**: 185–190.
16. Nijkamp FJ, Van Der Linde HJ, Folkerts G. Nitric oxide synthesis inhibitors induce airway hyperresponsiveness in the guinea pig *in vivo* and *in vitro*. *American Review of Respiratory Disease* 1993; **148**: 727–734.
17. Jolin Carlsson A, Bindslev L, Santesson J, Gottlieb I, Hedenstierna G. Hypoxic pulmonary vasoconstriction in the lung: the effect of prolonged unilateral hypoxic challenge during anaesthesia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 346–351.
18. Domino KB, Chen L, Alexander CM, Williams JJ, Marshall C, Marshall BE. Time course and responses of sustained hypoxic pulmonary vasoconstriction in the dog. *Anesthesiology* 1984; **60**: 562–566.
19. Vejlstrup NG, Dorrington KL. Intense slow hypoxic pulmonary vasoconstriction in gas-filled and liquid-filled lungs: an *in vivo* study in the rabbit. *Acta Physiologica Scandinavica* 1993; **148**: 305–313.
20. Glasser SA, Domino KB, Lindgren L, Parcella P, Marshall C, Marshall BE. Pulmonary blood pressure and flow during atelectasis in the dog. *Anesthesiology* 1983; **58**: 225–231.
21. Benumof JL. Intermittent hypoxia increases lobar hypoxic pulmonary vasoconstriction. *Anesthesiology* 1983; **58**: 399–404.
22. Chen L, Miller FL, Williams, JJ, Alexander CM, Domino KB, Marshall C, Marshall BE. Hypoxic pulmonary vasoconstriction is not potentiated by repeated intermittent hypoxia in closed chest dogs. *Anesthesiology* 1985; **63**: 608–610.
23. Bindslev L, Jolin A, Hedenstierna G, Bachrendtz S, Santeson J. Hypoxic pulmonary vasoconstriction in the human lung: effect of repeated hypoxic challenges during anesthesia. *Anesthesiology* 1985; **62**: 621–625.
24. Domino KB, Wetstein L, Glasser SA, Lindgren L, Marshall C, Harken AH, Marshall B. Influence of $P\bar{v}_{O_2}$ on blood flow to atelectatic lung. *Anesthesiology* 1983; **59**:428–434.
25. Elliott AR, Steffey EP, Jarvis KA, Marshall BE. Unilateral hypoxic pulmonary vasoconstriction in the dog, pony and miniature swine. *Respiration Physiology* 1991; **85**: 355–369.
26. Putensen C, Rasansen J, Downs JB. Effect of endogenous and inhaled nitric oxide on the ventilation–perfusion relationships in oleic-acid lung injury. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 330–336.
27. Rovira I, Chen TY, Winkler M, Kawai N, Bloch KD, Zapol WM. Effects of inhaled nitric oxide on pulmonary hemodynamics and gas exchange in an ovine model of ARDS. *Journal of Applied Physiology* 1994; **76**: 345–355.

British Journal of Anaesthesia 1996;77:419–420

SHORT COMMUNICATIONS

Influence of patient position on withdrawal forces during removal of lumbar extradural catheters

G. N. MORRIS, B. B. WARREN, E. W. HANSON, F. J. MAZZEO AND D. J. DIBENEDETTO

Summary

We have investigated the force required to remove lumbar extradural catheters from 88 parturients to determine the effects of patient positioning at removal, relative to the position at insertion. Parturients were allocated randomly to one of four groups: LS (lateral insertion, sitting withdrawal), LL (lateral insertion, flexed lateral withdrawal), SL (sitting insertion, lateral withdrawal) or SS (sitting insertion, sitting withdrawal). In both positions, the lumbar spine was kept maximally flexed. The force required to remove the catheter was measured at withdrawal. We found that the withdrawal force was influenced by the relationship between the position at removal and that at insertion, and we recommend that for ease of removal, patients should be placed in the same position as they were at the time of insertion. Compared with all other groups, the withdrawal force in patients in group LS was significantly greater ($P<0.05$). (*Br. J. Anaesth.* 1996;**77**:419–420)

Key words

Equipment, catheters extradural. Anaesthesia, obstetric.

Extradural catheters are usually removed without complications. However, there are reports of catheters that are difficult to remove, catheter breakage and shearing[1 3]. Fragments of catheter may be sequestered in the extradural space. Removal of an extradural catheter also has the potential for inducing extradural haematoma formation[4]. Hence, minimizing the extraction force is desirable. Previous studies have indicated that the force at extraction of lumbar extradural catheters was significantly greater with patients sitting compared with the lateral position[5 6]. These studies did not consider the position of the patient at insertion as an influencing factor. At insertion, the catheter is passed through a firm Tuohy needle and is held in a straight line to the extradural space. We hypothesized that if patients were placed in the same position for removal as they were at insertion, the catheter would again take a straight course and be less likely to be held by adjacent structures (lumbar fascia, vertebral arches and vertebral processes).

Methods and results

We studied 88 parturients at the University Hospital requesting analgesia for labour and delivery, Caesarean section, or both, using a standardized set (Baxter Healthcare Corporation, Cat. No. 2T0023). The study was approved by the Human Investigation Committee at the University of Virginia and informed consent was obtained from all patients. Patients were allocated randomly to one of four groups, depending on the position of the patient during insertion of the extradural catheter (sitting (S) or lateral (L)) and the position during removal of the catheter: LL, SS, LS or SL. Patients were ASA I or II and the usual exclusion criteria, including chronic low back ache or previous lumbar spine surgery, were applied.

All extradural catheters were inserted via the L2–3 or L3–4 intervertebral space using a 17-gauge Tuohy needle with loss of resistance to normal saline to identify the extradural space. A 19-gauge, styletted extradural catheter, with bullet tip and three lateral eyes, was threaded to allow 2–5 cm to remain in the extradural space. The position of the patient during insertion and removal was either lying in the lateral position or sitting with the legs over the edge of the bed, according to group allocation. In both positions the lumbar spine, hips and knees were kept maximally flexed. The catheter was left *in situ* until after vaginal or Caesarean section delivery. At removal, the catheter was connected to a portable force gauge using a knot tied at the 20–30-cm catheter mark, and slow incremental traction was applied in a direction perpendicular to the skin of the back. Peak tension during withdrawal was measured by a Normark digital force gauge (Normark Corporation, Minneapolis, MN, USA) with an accuracy to within 0.56 Newtons (N). The investigator who inserted the catheter also removed the catheter in all but three cases, when they were removed by another investigator. All catheters were removed intact, without stretching or kinking. The duration that the catheter was in place (h), depth of the lumbar extradural space from the skin and length of the catheter left *in situ* just before withdrawal (SD 0.5 cm), were noted.

Patient data were comparable in the four groups (table 1). Ten unused catheters were clamped at the tip and tested for break strength using the same equipment.

Data were analysed by Kruskal–Wallis one-way analysis of variance, followed by Dunn's method for pairwise multiple comparison, using SigmaStat

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Table 1 Patient data (mean (SD or range)) and extradural catheter withdrawal force (mean (SD) and median). Groups LL, SS, LS and SL = position of patient at catheter insertion and removal, where the first letter refers to insertion (lateral (L) or sitting (S)) and the second to removal (lateral (L) or sitting (S)). $* P < 0.05$, LS compared with LL, SS and SL

	Group LL	Group SS	Group LS	Group SL
n	21	23	22	22
Age (yr)	24.9 (15–36)	25.08 (16–40)	25.27 (15–44)	23.8 (16–35)
Height (m)	1.69 (0.06)	1.64 (0.05)	1.64 (0.05)	1.62 (0.07)
Weight (kg)	73.06 (14.25)	81.65 (20.85)	76.93 (14.34)	78.96 (21.58)
Length of catheter in extradural space (cm)	3.55 (0.59)	3.67 (0.67)	3.5 (0.74)	3.8 (0.73)
Depth of catheter in extradural space (cm)	4.98 (1.49)	6.04 (2.01)	5.73 (1.16)	5.61 (1.63)
Duration of catheter in extradural space (h)	5.92 (5.5)	10.0 (6.02)	7.11 (4.81)	5.9 (2.48)
Force required to remove extradural catheter				
Mean force (N)	1.71 (0.84)	2.04 (1.03)	3.17 (1.22)	1.25 (0.84)
Median force (N)	1.67	1.95	3.33*	0.97

(Jandel Scientific Software, San Rafael, CA, USA). $P<0.05$ was considered statistically significant. The power of the study was 0.79 (where difference in group mean to be detected was 1.0, expected SD of results=1.0, number of groups=4, group size=22 and $\alpha=0.05$). The force required to remove the catheters in group LS (lateral position at insertion, sitting position at removal) was significantly greater compared with all other groups (table 1). Comparison between the other groups revealed no significant differences. The greatest recorded force occurred in group LS (5.8 N). The mean break strength of 10 extradural catheters was 15.9 N, breakage occurring at the site of one of the three lateral eyes in all instances.

Comment

Minimizing the force at extraction of an extradural catheter may reduce the risk of breakage with sequestration. Previous studies advocated the lateral position for ease of removal[5,6] without considering the position of the patient at the time of insertion of the catheter. In this study we standardized all variables except that of position at insertion and removal.

We determined that significantly greater force was required to remove catheters in group LS compared with all other groups. Thus our findings agree with those of Boey and Carrie[4] who found that when catheters were inserted with patients in the lateral position, less force was needed if they were also removed in this position (group LL). We also identified a difference between groups LS and SS (different positions at insertion, both sitting at withdrawal) confirming the importance of the position of the patient at insertion in relation to the position at withdrawal, a fact that has not been documented previously. There was no detectable difference between groups SS and LL, implying that the sitting position at removal *per se* did not result in an elevated extraction force if the catheter was also inserted in this position. These are the groups in which the catheter was most likely to be held in a straight course at both insertion and removal. However, the significant difference between groups LS and SL (the position at removal differs from that at insertion in both groups) cannot be explained by a more tortuous course of the catheter alone, and indicates additional influencing factors.

We noted a large difference between the maximum recorded force at removal (5.8 N) and break strength of the catheters used (15.9 N). The weakest point of the catheter was at the site of the side wall perforations. However, should partial shearing occur inadvertently by manipulation of the catheter while the Tuohy needle is in place, the break strength may be reduced considerably.

In summary, the force required to remove lumbar extradural catheters was affected by the position of the patient both at insertion and removal. We agree with previous investigators that when an extradural catheter is placed with the patient in the lateral position, the withdrawal force is significantly elevated when this patient is seated at the time of removal[5,6]. However, when a catheter is placed in the sitting position, our results indicated that removal in this same position required no extra force. The position of the patient at extraction in relation to the position at insertion is an influencing factor which has not been recognized previously. Therefore, if resistance or stretching of the catheter occurs while attempting withdrawal, we recommend placing patients in the same position as they were at the time of insertion.

References

1. Tio TO, Macmurdo SD, McKenzie R. Mishap with an extradural catheter. *Anesthesiology* 1979; **50**: 260–262.
2. Lenox WC, Kost-Byerly S, Shipley R, Yaster M. Pediatric caudal extradural catheter sequestration: An unusual complication. *Anesthesiology* 1995; **83**: 1112.
3. Staats PS, Stinson MS, Lee RR. Lumbar stenosis complicating retained extradural catheter tip. *Anesthesiology* 1995; **83**: 1115–1118.
4. Klement W, Rothe G, Peters J. Paraplegia after removal of an extradural catheter. *Regional Anaesthesia* 1991; **14**: 88–91.
5. Boey SK, Carrie LES. Withdrawal forces during removal of lumbar extradural catheters. *British Journal of Anaesthesia* 1994; **73**: 833–835.
6. Blackshear RH, Gravenstein N, Radson E. Tension applied to lumbar extradural catheters during removal is much greater with patient sitting versus lying. *Anesthesiology* 1991; **75**: A833.

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Effect of oral antihistamine premedication on mivacurium-induced histamine release and side effects†

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Summary

In this randomized, double-blind, placebo-controlled study, we have examined histamine release, haemodynamic and cutaneous effects of mivacurium administered in low (0.105 mg kg^{-1}=1.5×ED_{95}) and high (0.21 mg kg^{-1}=3×ED_{95}) doses and assessed if oral pretreatment with H_1/H_2 antagonists would blunt the effects of mivacurium-induced histamine release. Patients received either ranitidine 300 mg and dimethindene 0.1 mg kg^{-1} (H_1 blocker) or placebo, orally 1 h before induction of anaesthesia. Twelve patients were allocated to each group. Although plasma concentrations of histamine increased significantly in three patients in the placebo group given low-dose mivacurium, the mean value for the group was unchanged. Plasma concentrations of histamine increased significantly in five patients in the placebo group after high-dose mivacurium and the mean value was increased. There was no consistent correlation between haemodynamic changes, cutaneous manifestations and histamine concentrations. Significant cardiovascular reactions occurred in six patients in the placebo groups and in only one patient treated with antihistamines. (*Br. J. Anaesth.* 1996;**77**:421–423)

Key words

Neuromuscular block, mivacurium. Histamine. Histamine, antihistamines. Premedication, ranitidine. Premedication, dimethindene.

Mivacurium is a non-depolarizing neuromuscular blocking agent with a relatively short duration of action. Increasing the dose of mivacurium may speed the onset of neuromuscular block, but may also increase histamine release and adverse haemodynamic effects[1 2]. Previous studies have shown that prophylactic use of i.v. antihistamines can attenuate many of the histamine-mediated side effects of atracurium[3]. In this randomized, double-blind, placebo-controlled study, we have investigated if oral antihistamines are effective in reducing the histamine-related side effects of mivacurium.

Methods and results

After obtaining approval from the hospital's Ethics Committee and written informed consent, we studied 48 ASA I-II patients of both sexes, aged 18–65 yr, weighing 45–100 kg, undergoing elective surgery. Subjects were allocated randomly to one of four groups. All patients received premedication with lormetazepam 2 mg orally, 1–2 h before induction of anaesthesia. One hour before induction of anaesthesia, patients received either ranitidine 300 mg and dimethindene 0.1 mg kg^{-1} or placebo orally. Anaesthesia was induced with thiopentone 5–7 mg kg^{-1} and maintained by spontaneous breathing of a mixture of 0.8–1.5% enflurane and 66% nitrous oxide in oxygen via a face mask. Six minutes after administration of thiopentone, mivacurium 0.105 mg kg^{-1} or 0.21 mg kg^{-1} was given over 30 s. Administration of drugs in our study differed from that of routine clinical practice in that there was a temporal delay of approximately 6 min between administration of thiopentone and neuromuscular block. This was done intentionally so that we might examine the individual effects of the two drugs.

Blood was obtained for measurement of plasma concentrations of histamine 1 min before administration of thiopentone, 3 and 5 min after thiopentone, and 3 and 5 min after mivacurium. Plasma concentrations of histamine were measured using the fluorometric enzymatic method[4]. Heart rate was measured continuously by ECG. Systemic arterial pressure was recorded by periodic, non-invasive measurement by an oscillation method (Dinamap, Critikon) every 1 min. Changes in arterial pressure or heart rate were considered significant if they deviated 20% from baseline values. We identified the most significant changes in arterial pressure or heart rate within the first 5 min of drug administration as peak levels. An investigator blinded to the study assessed cutaneous manifestations of histamine release on a scale described previously[5].

Data are presented as mean (SD). Data were analysed using the Mann–Whitney *U* and Wilcoxon tests. The effects of antihistamines in preventing mivacurium-induced flush were analysed by Fisher's exact test and the Mantel–Haenszel test, which permits combination of chi-square data[6].

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There were no significant differences between the treated and placebo groups in age, weight, type of procedure or ASA classification (grades I or II).

Thiopentone alone caused similar decreases in arterial pressure and heart rate in both groups. Mean plasma concentrations of histamine did not increase after administration of thiopentone. While five patients in the placebo group and three in the antihistamine group had increased concentrations, there was no correlation between these changes and hypotension and flush (see table 1).

Comment

Plasma concentrations of histamine increased significantly in three patients in the placebo group given low-dose mivacurium, although the mean value was unchanged. After high-dose mivacurium, histamine concentrations were increased in five patients in the placebo group, and mean values increased from baseline values of 0.59 (0.56) to 5.91 (12.31) ng ml^{-1}. Antihistamines decreased mivacurium-induced histamine release. We had observed previously that pretreatment with similar regimens of i.v. antihistamines significantly reduced histamine concentrations 2 min after administration of atracurium (0.24 *vs* 0.38 ng ml^{-1}; $P<0.04$)[5]. Our results using oral antihistamines were even more dramatic. In those patients pretreated with antihistamines receiving high-dose mivacurium, however, the increase in mean plasma histamine concentrations was significantly attenuated (0.76 (1.14) *vs* 5.32 (12.22) ng ml^{-1}; $P\leq0.04$). We suggest therefore that in addition to receptor antagonism, another significant effect of antihistamines may be to inhibit drug-induced histamine release.

Heart rate and systolic arterial pressure did not differ significantly between the placebo and treatment groups after administration of mivacurium. In the treated group, only one patient (No. 21) showed significant cardiovascular changes after either low- or high-dose mivacurium, even in the presence of increased histamine concentrations. However, four patients in the placebo group exhibited significant tachycardia after high-dose mivacurium (table 1).

Table 1 Relationship between histamine concentrations (ng ml^{-1}) (before (baseline (B)) and after mivacurium (M)) and systolic arterial pressure (SAP), heart rate (HR) and cutaneous manifestations. Individual values are shown only for patients exhibiting significant cardiovascular changes or cutaneous manifestations, although mean (SD) values are shown for each treatment group. Values indicate peak concentrations or concentrations obtained after mivacurium. *Significant changes in histamine concentration compared with baseline; †significant changes (> 20%) in SAP and HR compared with baseline. F = flush

Patient No	Histamine concentration		SAP		HR		
	B	+3/+5 min after M	B	+2/+4 min after M	B	+2/+4 min after M	Cutaneous reactions after M (flush)
Premedication: placebo (n=11) – mivacurium 1.5xED_{95} – peak values							
6	1.20	0.69	132	117	95	90	F (+ 1 min)
15	0.67	0.33	142	113†	77	73	F (+ 1 min)
20	0.84	1.26*	135	124	101	84	F (+ 2 min)
26	0.63	1.05*	117	111	102	86	
34	0.13	0.09	131	110	112	95	F (+ 1 min)
46	0.19	3.07*	124	102	83	70	
(n=11)	0.63 (0.43)	0.75 (0.85)	120 (9)	108 (8)	85 (11)	85 (13)	
Premedication: placebo (n=12) – mivacurium 3xED_{95} – peak values							
2	1.86	1.86	112	109	72	89	F (+ 1 min)
4	1.60	21.07*	105	89	79	104†	F (+ 1 min)
10	0.66	0.78	121	105	79	87	F (+ 2 min)
11	0.46	1.45*	113	69†	93	101	F (+ 1 min)
19	0.25	0.43*	120	125	96	83	F (immediate)
24	0.37	0.45	118	110	74	93†	F (+ 1 min)
31	0.30	0.57	137	120	76	81	F (+ 1 min)
44	0.39	40.30*	130	75†	80	111†	Pronounced flush
45	0.22	3.37*	127	111	75	109†	F (+ 1 min)
(n=12)	0.59 (0.56)	5.91 (12.31)	116 (12)	105 (20)	88 (10)	93 (14)	
Premedication: $H_1 + H_2$ receptor antagonists (n=11) – mivacurium 1.5xED_{95} – peak values							
5	1.50	10.11*	137	115	99	73	
8	0.33	0.31	146	127	88	109	F (+ 1 min)
35	0.33	0.63*	121	138	95	102	
40	0.36	3.03*	116	104	70	76	
(n=11)	0.46 (0.38)	1.45 (2.99)	115 (9)	115 (17)	86 (10)	85 (1)	
Premedication: $H_1 + H_2$ receptor antagonists (n=12) – mivacurium 3xED_{95} – peak values							
9	0.60	0.84	119	104	91	80	F (+ 1 min)
14	0.19	0.52	124	117	94	102	F (+ 1 min)
21	0.24	1.05*	132	93†	94	96	
23	0.16	1.14*	136	108	91	76	F (+ 1 min)
25	0.39	4.17*	137	127	103	112	F (+ 1 min)
48	0.30	0.78*	111	116	89	105	
(n=12)	0.55 (0.62)	1.32 (1.47)	113 (11)	112 (15)	92 (13)	92 (13)	

In addition, two patients in the placebo group showed a marked decrease in systolic arterial pressure after high-dose mivacurium. In patient No. 4, heart rate increased (from 79 to 104 beat min^{-1}) coincident with a histamine concentration of 21.07 ng ml^{-1}, although there was no significant decrease in arterial pressure. In patient No. 44, arterial pressure decreased from 130/58 to 75/40 mm Hg after high-dose mivacurium. Six patients, all in the placebo group, showed evidence of significant histamine release without any evidence of hypotension. Neither the frequency nor extent of hypotension after administration of mivacurium were correlated significantly with histamine concentrations.

After low-dose mivacurium, a flush was seen in five patients, four of whom were in the placebo group (table 1). After high-dose mivacurium, the number of cutaneous reactions increased in both groups; nine in the placebo and four in the treated group. Although antihistamines did not influence the likelihood of flush after either low- or high-dose mivacurium (two-tailed Fisher's exact test, P=0.31 and P=0.09, respectively), when data from low- and high-dose mivacurium were combined there was convincing evidence for such protection (Fisher's exact test, P=0.03). Using the more definitive Mantzel–Haenszel test, the likelihood of flush in the antihistamine group compared with the placebo group was 0.25 and 0.44 (95% CI 0.32–1.89 and 0.18–1.05) for low- and high-dose mivacurium, respectively, and 0.38 (95% CI 0.17–0.86) when the data were combined.

Six of the seven significant cardiovascular changes observed were accompanied by flush, and four of the six exhibited concomitant increases in plasma concentrations of histamine. However, our findings, and those of our previous atracurium study[3], suggest that many patients flush without cardiovascular changes. In this study, flush occurred in 13 patients in the placebo group, although plasma histamine concentrations increased without flush or cardiovascular changes in two patients. We postulate that not all cutaneous manifestations associated with mivacurium are directly attributable to histamine release and thus may not be prevented by antihistamines.

Our results may have clinical implications. While significant hypotension occurred in three patients in the placebo group, only one of the antihistamine-treated patients sustained significant hypotension despite evidence of histamine release. In most patients, oral pretreatment with H_1 and H_2 antagonists appeared to be effective against mivacurium-induced rash or flush. It is well known that slow injection or the use of low doses of mivacurium may reduce histamine release after administration of mivacurium. Our results indicate that the use of oral H_1 and H_2 receptor antagonists represents another option for clinicians to prevent or at least reduce histamine-related side effects after administration of high-dose mivacurium.

References

1. Savarese JJ, Ali HH, Basta SJ, Scott RPF, Embree PB, Wastila WB, Abou-Donia MM, Gelb C. The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide–opiate–barbiturate anesthesia. *Anesthesiology* 1989; 70: 386–394.
2. Savarese JJ, Ali HH, Basta SJ, Embree PE, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology* 1988; 68: 723–732.
3. Doenicke A, Moss J, Lorenz W, Hoernecke R, Gottardis M. Are hypotension and rash after atracurium really caused by histamine release? *Anesthesia and Analgesia* 1994; 78: 967–972.
4. Lorenz W, Neugebauer E. Current techniques of histamine determination: fluorometric assays. In: Uvnäs B, ed. *Histamine and Histamine Antagonists (Handbook of Experimental Pharmacology), vol. 97.* Berlin: Springer Verlag, 1991; 385–439.
5. Doenicke A, Moss J, Lorenz W, Hoernecke R. Morphine iv and nalbuphine iv cause histamine and catecholamine increase without relevant hemodynamic changes. *Clinical Pharmacology and Therapeutics* 1995; 58: 81–89.
6. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959; 22: 719–748.

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Edrophonium and human plasma cholinesterase combination for antagonism of mivacurium-induced neuromuscular block

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Summary

We have compared the reversal characteristics of mivacurium after administration of an edrophonium–plasma cholinesterase (PCHE) combination with that produced by each antagonist alone. Forty ASA I adults were given mivacurium 0.15 mg kg^{-1} during fentanyl–thiopentone–nitrous oxide–isoflurane anaesthesia. TOF stimulation was applied to the ulnar nerve every 12 s, and the force of contraction of the adductor pollicis muscle was recorded. When spontaneous recovery of first twitch height (T1) reached 10% of its initial control value, patients were allocated randomly to one of four groups (n=10 in each). Neuromuscular function in patients in group 1 (control group) was allowed to recover spontaneously. Patients in groups 2–4, respectively, received edrophonium 1 mg kg^{-1} (group ED), exogenous PCHE equivalent to activity present in 25 ml kg^{-1} of human plasma (group PCHE) or edrophonium 1 mg kg^{-1} with exogenous human PCHE equivalent to the activity present in 25 ml kg^{-1} of human plasma (combination group). The time to attain a TOF ratio of 0.75 in the combination group was 4.6 (SD 0.9) min. This was shorter (P<0.01) than that observed in patients in the control (16.8 (3.3) min), ED (8.9 (3.6) min) and PCHE (9.3 (1.6) min) groups. There was no difference in recovery indices between groups ED and PCHE. We have demonstrated that the edrophonium–PCHE combination significantly accelerated recovery of mivacurium-induced block compared with that observed with the use of individual antagonists. (*Br. J. Anaesth.* 1996;**77**:424–426)

Key words

Antagonists, enzyme, plasma cholinesterase. Antagonists, neuromuscular block, edrophonium. Monitoring, neuromuscular function. Neuromuscular block, mivacurium. Neuromuscular block, measurement of response.

Mivacurium chloride is a bis-benzylisoquinolinium non-depolarizing neuromuscular blocking agent[1]. Spontaneous recovery from 90% mivacurium block to 95% twitch height and train-of-four (TOF) of 0.75 normally occurs within 15 min[2]. We noted that these recovery times can be shortened by administration of edrophonium, neostigmine or human plasma cholinesterase (PCHE)[2 3].

Although both PCHE and edrophonium produce dose-dependent antagonism of mivacurium-induced block[2 4], each drug acts by a different mechanism. PCHE is an enzyme that enhances hydrolysis of mivacurium in plasma, whereas edrophonium (an anticholinesterase) acts mainly by increasing the concentration of acetylcholine in the end-plate region of the muscle. These differences in pharmacodynamic characteristics might confer some advantages in combining the two drugs in clinical practice. Accordingly, we have compared the reversal characteristics of mivacurium after PCHE and edrophonium in combination with that produced by each drug alone.

Methods and results

After obtaining institutional approval and informed consent, we studied 40 ASA I patients of both sexes, aged 16–51 (mean 34) yr, weighing 52–85 kg (mean 68.8 (SD 8.9) kg). All patients were undergoing elective procedures, had no neuromuscular, renal or hepatic disease, and were not receiving any drug known to interfere with neuromuscular function.

All patients received lorazepam 2 mg orally, 90 min before operation. An infusion of lactated Ringer's solution was given i.v. before induction of anaesthesia. The electrocardiogram, haemoglobin oxygen saturation by pulse oximetry and arterial pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5± 0.5 °C. Anaesthesia was induced with fentanyl 2 μg kg^{-1} and thiopentone 3–5 mg kg^{-1}, and maintained with 70% nitrous oxide and 0.5% inspired isoflurane in oxygen. Concentrations of isoflurane, nitrous oxide, oxygen and carbon dioxide were measured continuously by a multiple-gas analyser (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide pressure 4.8–5.3 kPa).

Isoflurane was administered for 30 min before control twitch height was recorded. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2-ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant

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Table 1 Plasma cholinesterase (PCHE) activity, first twitch (T1) and train-of-four (TOF) recovery from 10% block ($n = 10$) (mean (SC)). [1] Blood sample obtained before induction of anaesthesia; [2] Blood sample obtained when TOF ratio had recovered to 0.75; [3] $n = 8$ patients, in the remaining two patients twitch recovery was > 25% after administration of edrophonium; [4] Twitch recovery was > 25% after administration of the PCHE-edrophonium combination in all patients. * $P < 0.0$[illegible] $P < 0.01$ compared with the spontaneous recovery group (Dunnett's mean comparison between the control and other groups [illegible] < 0.01 compared with other study groups (Tukey's Studentized range method for groups that received different antagonists)

Group	Antagonist	PCHE activity (first assay)[1] (ref. range = 7–19 iu ml^{-1})	PCHE activity (second assay)[2] (iu ml^{-1})	Percent change in PCHE activity	T1 at 10 min (% control)	TOF ratio at 10 min	Times to T1 recovery (min)		Time to TOF = 0.75 (min)
							25–75%	10–95%	
Group 1	—	13.3 (1.9)	13.2 (1.8)	−0.3 (1.8)	72.4 (13.7)	0.50 (0.11)	8.4 (3.0)	15.3 (4.7)	16.8 (3.3)
Group 2	Edrophonium 1 mg kg^{-1}	13.6 (2.2)	12.5 (1.6)††	−7.9 (6.3)	90.2 (12.7)**	0.77 (0.13)**	5.3 (3.4)[3]*	8.5 (3.5)**	8.9 (3.6)**
Group 3	PCHE 25 ml kg^{-1}	11.7 (2.5)	21.6 (3.9**	+86.4 (20)	98.8 (3.2)**	0.76 (0.06)**	3.9 (1.0)**	7.3 (1.5)**	9.3 (1.6)**
Group 4	PCHE 25 ml kg^{-1} + edrophonium 1 mg kg^{-1}	12.1 (1.2)	21.5 (1.5)**	+80.1 (23)	100 (0)**	0.88 (0.5)** ††	—[4]	5.7 (0.9)**	4.6 (0.9)** ††

contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). Preload tension on the thumb was maintained at 300 *g* throughout the study.

After a stable neuromuscular response was obtained for 10 min, the patient received mivacurium 0.15 mg kg^{-1} i.v. as a bolus dose. Tracheal intubation was performed when neuromuscular response was abolished. Additional increments of mivacurium 0.1 mg kg^{-1} were given to patients who required continued neuromuscular block whenever the first twitch recovered to 10% of the control value.

At the end of surgery, when first twitch height (T1) (the first response in the TOF) had recovered to 10% of control, patients were allocated randomly to one of four groups (n=10 in each). Neuromuscular function in patients in group 1 (control) was allowed to recover spontaneously, whereas patients in groups 2–4, respectively, received edrophonium 1 mg kg^{-1} (group ED), exogenous human PCHE equivalent to the activity present in 25 ml kg^{-1} of human plasma (group PCHE) or edrophonium 1 mg kg^{-1} with exogenous human PCHE equivalent to activity present in 25 ml kg^{-1} of human plasma (combination group). All drugs were given in 5 s into a rapidly flowing i.v. infusion. In the combination group (group 4), drugs were given simultaneously into two separate i.v. catheters inserted into one arm. Atropine 0.02 mg kg^{-1} was given to all patients who received edrophonium.

Serum cholinesterase P Behring was used in this study, which is a dry concentrate of highly purified enzyme. The contents of each vial (27–83 mg) are equivalent in activity to 500 ml of fresh normal human plasma. However, cholinesterase activity is standardized by the manufacturer. The purified human PCHE is derived from donor plasma, that is hepatitis B surfactant antigen-negative and anti-HIV-1-negative. It is pasteurized at 60 °C to inactivate DNA viruses. The risk of treatment with purified human PCHE is considered comparable with administration of human albumin.

The TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T4/T1) was recorded continuously in all patients until the TOF ratio recovered to 0.75 or more. Isoflurane was continued during this observation period. All patients were assessed in the recovery room, on admission and 10 min later, for signs of residual weakness by their ability to maintain 5-s head-lift, tongue protrusion and cough.

In all patients, two venous blood samples were obtained from an antecubital vein in the contralateral arm to that used for i.v. fluid administration for measurement of plasma cholinesterase activity. The first sample was obtained before induction of anaesthesia and the second when the TOF ratio had recovered to 0.75. Plasma cholinesterase activity was measured by the change in absorbance at 600 nm after hydrolysis of butyrylthiocholine to thiocholine, using Du Pont Dimension, Clinical Chemistry System (Wilmington, DE, USA).

Recovery times of the first twitch from 25% to 75% (recovery index) and from 10% to 95% of control, and time to a TOF ratio of 0.75 were compared using analysis of variance. Dunnett's test was used to compare the spontaneous recovery group with each of the other groups. Comparisons between groups that received different antagonists (groups 2–4) were carried out using Tukey's Studentized range method. All statistical analyses were carried out using BMDP statistical package, release 7.01 (University of California Press, Berkeley, CA, 1993). Unless otherwise specified, results are expressed as mean (SD). P<0.05 was considered statistically significant.

Baseline activity of PCHE was similar and within the normal range in all groups (reference range 7–19 iu ml^{-1}) (table 1). The activity in the second assay was greatest (P<0.01) in patients who received exogenous PCHE (groups 3 and 4) compared with those in groups 1 and 2.

Final T1 recovery was always within 10% of the initial control value. Indices of recovery are shown in table 1. The initial T1 recovery in all patients in the combination group and in two patients in group ED was >25% of control. The times taken for twitch height to recover from 25% to 75% and from 10% to 95% of control, and from 10% of control to a TOF=0.75 were significantly longer in patients in the control group compared with those in other groups (table 1). The time to attain a TOF ratio of 0.75 in the combination group was 4.6 (0.9) min. This was significantly shorter (P<0.01) than that observed in patients in groups ED and PCHE. There was no difference in recovery indices between groups ED and PCHE (table 1).

There was no indication of residual weakness in the recovery room after anaesthesia.

Comment

We have demonstrated that the time to attain a TOF ratio of 0.75 (after return to 10% first twitch height) was shorter ($P<0.01$) with a combination of edrophonium 1 mg kg^{-1} and exogenous human PCHE equivalent to activity present in 25 ml kg^{-1} of human plasma than that observed in patients in the control (16.8 (3.3) min), ED (8.9 (3.6) min) and PCHE (9.3 (1.6) min) groups. Further, both PCHE and edrophonium (in the doses used in this study and in patients with normal PCHE activity) had similar efficacy as antagonists of mivacurium-induced neuromuscular block (table 1).

The results of this study confirm our recently published data that administration of either edrophonium or exogenous PCHE equivalent to activity present in 25 ml kg^{-1} of human plasma results in reliable antagonism of mivacurium-induced neuromuscular block[2,3]. We have also demonstrated that when antagonism of mivacurium was attempted with edrophonium or PCHE alone, at 90% twitch depression, the time saved to return to TOF=0.75 compared with control was <8 min. However, with the use of the PCHE–edrophonium combination, mean time saved was >12 min.

Our data suggest that when recovery is established, residual mivacurium block is sensitive to both increases in PCHE activity and inhibition of acetylcholinesterase at the neuromuscular junction. The relative importance of both components cannot be determined from our study. Although the magnitude of recovery was similar after administration of either PCHE or edrophonium, the PCHE–edrophonium combination proved to be superior than any of the individual drugs alone. Each drug acts by a different mechanism. Increasing PCHE activity enhances hydrolysis of mivacurium in plasma. As the plasma concentration of mivacurium declines, there is net movement of mivacurium from the neuromuscular junction back into the blood. This accelerates recovery of neuromuscular function. In addition, inhibition of acetylcholinesterase at the neuromuscular junction facilitates recovery further. It should be noted, however, that the pharmacological action of edrophonium is not limited to inhibition of acetylcholinesterase. Evidence suggests that the direct influences of the acetylcholinesterase drugs on neuromuscular transmission involve at least three distinct, although possibly interacting mechanisms: (a) weak agonist action, (b) formation of desensitized receptor complex intermediates, and (c) alteration of the conductance properties of active channels[5].

The dose of PCHE equivalent in activity to 25 ml kg^{-1} of human plasma in a 65-kg patient represents, on average, the equivalent of PCHE activity of 1625 ml of adult human plasma. Serum cholinesterase P Behring concentrate is expensive, at approximately $US 300 for one vial, and the shelf-life is 2 yr. Therefore, the average cost of PCHE administered per patient in groups 3 or 4 is more than $US 1000. Nevertheless, because of the prohibitive cost of this compound, this reversal modality is unlikely to have a routine practical application at this time. A possible exception might be the individual who is homozygous for atypical butyrylcholinesterase[6].

References

1. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology* 1988; **68**: 723–732.
2. Naguib M, Abdulatif M, Al-Ghamdi A, Hamo I, Nouheid R. Dose–response relationships for edrophonium and neostigmine antagonism of mivacurium-induced neuromuscular block. *British Journal of Anaesthesia* 1993; **71**: 709–914.
3. Naguib M, Daoud W, El-Gammal M, Ammar A, Turkistani A, Selim M, Altamimi W, Sohaibani MO. Enzymatic antagonism of mivacurium-induced neuromuscular blockade by human plasma cholinesterase. *Anesthesiology* 1995; **83**: 694–701.
4. Naguib M, Selim M, Bakhamees HS, Samarkandi AH, Turkistani A. Enzymatic *versus* pharmacologic antagonism of profound mivacurium-induced neuromuscular blockade. *Anesthesiology* 1996 ;**84**;1051–1059.
5. Pascuzzo GJ, Akaike A, Maleque MA, Shaw K-P, Aronstam RS, Rickett DL, Albuquerque EX. The nature of the interactions of pyridostigmine with the nicotinic acetylcholine receptor–ionic channel complex. I. Agonist, desensitizing, and binding properties. *Molecular Pharmacology* 1984; **25**: 92–101.
6. Naguib M, El-Gammal M, Daoud W, Ammar A, Moukhtar H, Turkistani A. Human plasma cholinesterase for antagonism of prolonged mivacurium-induced neuromuscular blockade. *Anesthesiology* 1995; **82**: 1288–1292.

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Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs†

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Summary

We have studied the effect of dexmedetomidine during coronary artery stenosis (CAS) in dogs. Three periods of 15 min of CAS were induced at 40-min intervals in two groups of dogs (dexmedetomidine compared with placebo). Dexmedetomidine was administered before the second and third periods of CAS in doses of 1 and 3 µg kg^{-1}, respectively. Dexmedetomidine decreased plasma concentrations of noradrenaline by mean 71 (SEM 9) %, heart rate by 8 (4) %, cardiac output by 30 (6) % and increased mean arterial pressure by 23 (10) %. Dexmedetomidine reduced blood flow in non-ischaemic myocardium and in the ischaemic epicardial layer by 16 (8) %, but blood flow was preserved in the ischaemic mid-myocardial and subendocardial layers. Consequently, dexmedetomidine increased the ischaemic–non-ischaemic blood flow ratio. Dexmedetomidine did not change myocardial oxygen consumption but decreased myocardial oxygen demand from 4.91 (0.33) to 3.76 (0.25) µmol min^{-1} g^{-1}, thereby reducing the oxygen deficiency of the ischaemic myocardium from 1.47 (0.37) to 0.29 (0.32) µmol min^{-1} g^{-1}. (*Br. J. Anaesth.* 1996;**77**:427–429)

Key words

Sympathetic nervous system, adrenergic agonists. Heart, myocardial function. Sympathetic nervous system, dexmedetomidine. Heart, ischaemia. Heart, blood flow, myocardial. Dog.

Preliminary studies suggest that perioperative use of dexmedetomidine may result in a decreased risk of adverse cardiac events, including myocardial ischaemia[1]. This probably depends on a centrally mediated sympatholytic effect which decreases catecholamine-mediated stress responses. In contrast with these beneficial central effects, α_2 agonists may also cause peripheral and coronary vasoconstriction by stimulation of postjunctional α_2 adrenergic receptors. The effect of this vasoconstriction during myocardial ischaemia is controversial. Heusch and Deussen presented evidence that α_2 adrenoreceptor activation can worsen ischaemia[2]. In contrast, other investigators reported that α adrenoreceptor stimulation can beneficially modulate coronary blood flow during myocardial ischaemia by preventing transmural redistribution of blood flow away from ischaemic endocardium[3].

The aim of this study was to determine if systemic dexmedetomidine has beneficial effects on ischaemic myocardium in an animal model known to be highly sensitive to the direct, peripheral vasoconstrictor effect of α_2 agonists.

Methods and results

After obtaining animal Ethics Committee approval, mongrel dogs were anaesthetized with pentobarbitone and their lungs ventilated with 1% halothane and nitrous oxide in oxygen. The dogs were instrumented, as described previously[4], to measure aortic and left ventricular pressure and cardiac output. A cuff was placed on the left descending coronary artery (LAD). Coronary pressure was measured distal to the cuff. The degree of stenosis was controlled by keeping constant mean perfusion pressure distal to the stenosis using a Servo system feeding a motor pump, which determined the degree of cuff inflation. Global myocardial oxygen demand was estimated using the pressure–work index[5]. Regional oxygen consumption was measured from blood flow (radioactive microspheres) and local arterial–coronary venous oxygen content difference. Oxygen deficiency was calculated by subtracting oxygen consumption from oxygen demand.

Five minutes before the first period of CAS, control blood samples were obtained and haemodynamic measurements were performed. Thereafter, CAS 1 was induced by reducing mean pressure in the LAD distal to the stenosis to 40% of mean arterial pressure. After 12 min of stenosis, microspheres were injected. Two minutes later, blood samples were obtained and haemodynamic measurements performed. Thereafter, the CAS was released. Twenty minutes after release of the stenosis, measurements were repeated, followed by administration of dexmedetomidine 1 µg kg^{-1} in the active drug group (n=11) and saline in the placebo group (n=9). Twenty minutes after administration of dexmedetomidine, measurements were repeated followed by a second period of stenosis. Measurements during stenosis and the subsequent recovery period were the same as during the first episode of stenosis. This procedure was repeated a third time after administration of dexmedetomidine 3 µg kg^{-1} in the drug group.

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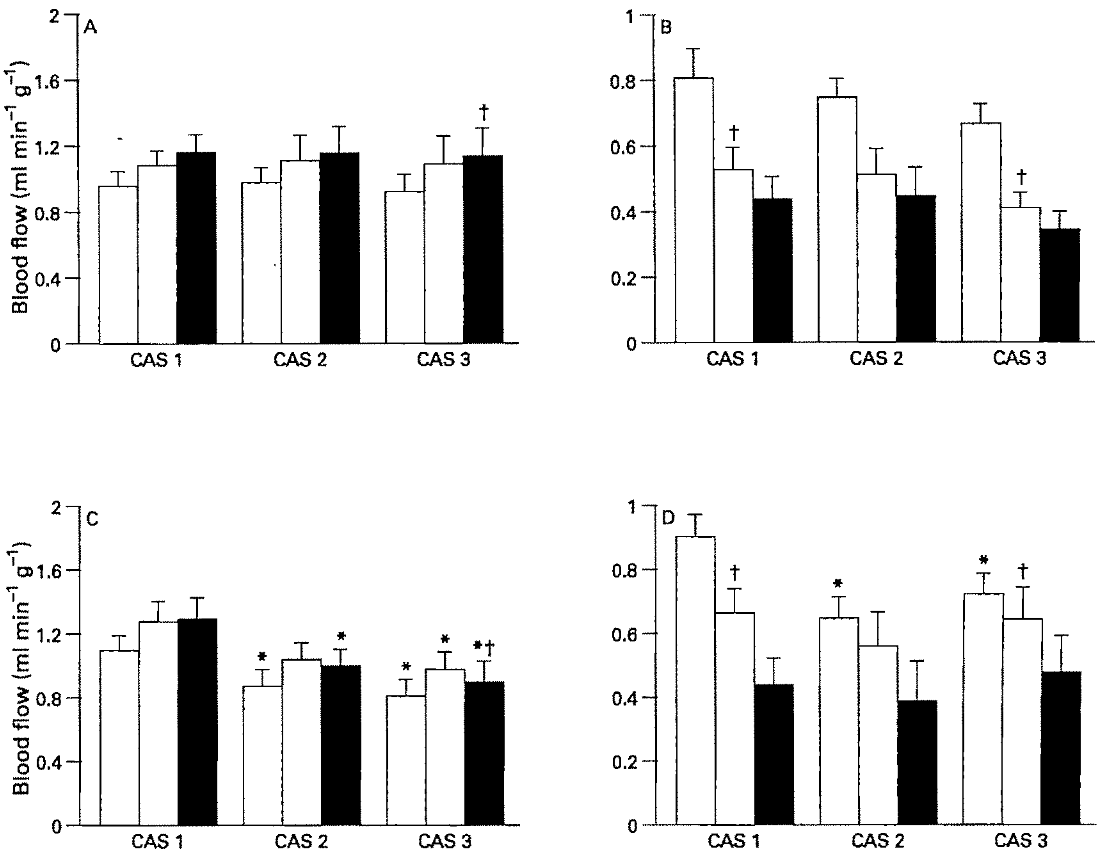

Figure 1 Regional blood flow distribution in non-ischaemic (left, A and C) and ischaemic (right, B and D) myocardium in the placebo (upper, A and B) and drug (lower, C and D) groups, measured with radioactive microspheres. Transmural samples were obtained from the perfusion area of the LAD (ischaemic myocardium) and from the posterior wall and interventricular septum (non-ischaemic myocardium). Samples were divided into subendocardial, mid-wall and subepicardial layers. In this way, coronary blood flow was measured simultaneously in non-ischaemic and ischaemic myocardium during the three stenoses. Shaded bars=epicardial flow; open bars=mid-myocardial flow; solid bars=endocardial flow. CAS=Coronary artery stenosis. Data are mean (SEM); *n*=9 in the placebo group, *n*=11 in the drug group. *Significantly different from corresponding CAS 1 value; †significantly different from corresponding value in other group.

Two-way ANOVA for repeated measures was used for inter-group comparisons. Intragroup comparisons were evaluated using one-way ANOVA for repeated measures and Fisher's protected LSD test as *post hoc* test. Baseline values between the two groups were compared using Student's *t* test. $P<0.05$ was considered significant. Results are expressed as mean (SEM).

Dexmedetomidine decreased heart rate (from 126 (6) to 114 (5) beat min^{-1}), d*P*/d*t*max (from 1371 (128) to 1177 (62) mm Hg s^{-1}) and cardiac output (from 4.2 (0.3) to 2.4 (0.4) litre min^{-1}) and increased mean arterial pressure (from 81 (4) to 98 (4) mm Hg) and systemic vascular resistance (from 1572 (131) to 3902 (563) dyn s cm^{-5}). In the placebo group, no haemodynamic changes were observed throughout the study.

Dexmedetomidine decreased plasma concentrations of noradrenaline from 121 (17) to 25 (12) pg ml^{-1}.

After dexmedetomidine 3 μg kg^{-1}, ischaemic–non-ischaemic blood flow ratios were significantly higher in the epicardial (from 0.81 (0.07) to 0.93 (0.09) and endocardial (from 0.33 (0.06) to 0.47 (0.10) layers compared with placebo (fig. 1).

Dexmedetomidine increased haemoglobin concentration from 7.2 (0.2) to 8.4 (0.3) mmol litre^{-1} and decreased myocardial oxygen demand from 4.91 (0.33) to 3.76 (0.25) μmol min^{-1} g^{-1}. Regional myocardial oxygen consumption did not change after dexmedetomidine (from 3.08 (0.39) to 3.20 (0.51) μmol min^{-1} g^{-1}). Dexmedetomidine decreased myocardial oxygen deficiency from 1.47 (0.37) to 0.29 (0.32) μmol min^{-1} g^{-1}.

Comment

In this study, dexmedetomidine decreased myocardial oxygen demand and reduced blood flow in non-ischaemic myocardium. This was related to its haemodynamic effects; reduction in heart rate and d*P*/d*t*max. Blood flow in the ischaemic inner layers was preserved. In this way, the ischaemic–non-ischaemic blood flow ratio decreased and myocardial oxygen deficiency was reduced.

The effects of dexmedetomidine on regional blood flow in ischaemic myocardium are in accordance with studies on the effects of aspecific α block or stimulation during ischaemia[5]. Preservation of blood flow in ischaemic myocardium by α_2 agonists is probably caused by more powerful local metabolic stimuli during ischaemia, which overrule adrenergic vasoconstriction. As the degree of ischaemia is most severe in the inner layers during hypoperfusion, adrenergic vasoconstriction in this region is inhibited to a greater extent than in the outer layer.

Distal to a flow-limiting stenosis, such specific epicardial vasoconstrictive effect may lead to improvement in endocardial perfusion, the "reverse steal" effect[3]. The decrease in heart rate after dexmedetomidine could be an additional explanation for this beneficial effect on blood flow, because slowing of the heart rate favours endocardial relative to epicardial perfusion. The different findings of Heusch and Deussen[2] who found that α_2 adrenergic activation can worsen myocardial ischaemia, may be explained by differences in preparation, degree of ischaemia, anaesthesia, and intensity and mode of α adrenergic stimulation.

Our preparation was expected to be highly sensitive to the direct, peripheral vasoconstrictor effects of dexmedetomidine[4]. Compared with humans, we therefore may have overestimated the coronary vasoconstrictive effects and underestimated the central sympatholytic effects of dexmedetomidine. This could also underestimate a possible anti-ischaemic effect of dexmedetomidine, because it was shown that systemic clonidine had anti-ischaemic properties, while intracoronary administration caused vasoconstriction[6]. However, these results should be extrapolated with caution to potential clinical use in humans as the results relate only to halothane-anaesthetized dogs. Halothane not only has marked haemodynamic effects, but could also have influenced the sympathetic responses.

Acknowledgements

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References

1. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, Mangano DT, The Study of Perioperative Ischemia Research Group. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. *Anesthesiology* 1995; **82**: 620–633.
2. Heusch G, Deussen A. The effects of cardiac sympathetic nerve stimulation on perfusion of stenotic coronary arteries in the dog. *Circulation Research* 1983; **53**: 8–15.
3. Nathan HJ, Feigl EO. Adrenergic vasoconstriction lessens transmural steal during coronary hypoperfusion. *American Journal of Physiology* 1986; **19**: H645–H653.
4. Roekaerts PMHJ, Prinzen FW, Willigers HMM, de Lange S. The effects of alpha$_2$-adrenergic stimulation with mivazerol on myocardial blood flow and function during coronary artery stenosis in anesthetized dogs. *Anesthesia and Analgesia* 1996; **82**: 702–711.
5. Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. *Circulation Research* 1978; **42**: 79–86.
6. Heusch G, Schipke J, Thamer V. Clonidine prevents the sympathetic initiation and aggravation of poststenotic myocardial ischemia. *Journal of Cardiovascular Pharmacology* 1985; **7**: 1176–1182.

British Journal of Anaesthesia 1996;77:430–431

CASE REPORT

An iatrogenic arterial foreign body

U. S. SHAH, R. DOWNING AND I. DAVIS

Summary

The creation, possible complications and retrieval of an unusual, perhaps unique, arterial foreign body are described. (*Br. J. Anaesth.* 1996;**77**:430–431)

Key words

Monitoring, arterial pressure. Arteries, cannulation. Complications, foreign body.

Case report

The patient was a right-handed, 72-yr-old woman undergoing internal fixation of a pathological fracture of the left femur by interlocking nail. Ten months before operation she had undergone a total left knee replacement under spinal and light general anaesthesia without incident. Three months before operation she had a left pneumonectomy for lung cancer: her early postoperative course was stormy as within hours of surgery she developed respiratory failure and atrial fibrillation, and required ventilation. Tracheotomy was performed and she was weaned from ventilatory support over the next 2 weeks. She was discharged with a prescription for domiciliary oxygen, and digoxin, verapamil and bumetanide. While walking at home she sustained a mid-shaft fracture of her left femur and was admitted for surgical fixation. She was in hospital for 1 week before operation during which time diclofenac and sustained-release morphine were added to her drug regimen.

At the preoperative visit she was sitting upright breathing oxygen from a face mask with her left leg in traction. She was dyspnoeic on slight exertion (moving herself in bed, eating lunch) and spoke in short sentences. She was orthopnoeic at about 45° and physically weak with a thoracolumbar kyphoscoliosis and sacral sores. Her haemoglobin concentration was 9.9 g dl^{-1} and serum albumin concentration 24 g $litre^{-1}$, but all other haematological and biochemical variables were normal.

The planned operation was estimated to take 2 h and required a supine patient. General anaesthesia was used with lumbar extradural block for intra- and postoperative pain management. The procedure took 3 h and involved transfusion of 4 u. of blood after which her lungs were ventilated electively overnight and her trachea extubated without difficulty the next morning.

A left subclavian central venous catheter and left radial arterial cannula were inserted to facilitate monitoring and management. The arterial cannula was a 20-gauge Ohmeda arterial catheter with Flo Switch (1 mm in diameter by 45 mm in length). The device is designed to be sewn to the skin by means of a fenestrated plate, with holes for two sutures, which is integral with the hub of the cannula. Insertion of a third suture to hold the cannula firmly at the junction of the hub and catheter sections led to a jet of blood from the cannula wound indicating some damage to the device. A 0.5-mm by 20-cm guidewire was inserted through the hub of the arterial cannula with the intention of withdrawing the device while maintaining vascular access, but the wire emerged from the cannula 2 mm from the hub which was then seen to have been completely severed from the catheter section (fig. 1). As a pulsatile jet of arterial blood continued to issue from the cannula wound, it seemed possible that the detached fragment might be protruding from the vessel wall. However, a cutdown showed the bleeding came from the arteriotomy wound indicating the catheter section of the cannula was wholly within the arterial lumen. Firm pressure was applied to the wound and a right radial arterial cannula was inserted. A vascular surgical opinion was sought.

While the left hand appeared pink and warm and had a good pulse oximeter signal, with saturation readings from the index finger identical to those from the right hand, it was felt that the risk of digital ischaemia from embolization by a large foreign body, and possible later infection, was unacceptable. The arteriotomy site was re-explored and the palmar arch searched using a Fogarty embolectomy catheter without result. The detached fragment of the cannula was finally delivered from the radial artery proximal to the point of its insertion by means of the Fogarty catheter. The surgical arteriotomy was closed with 6/0 Prolene sutures.

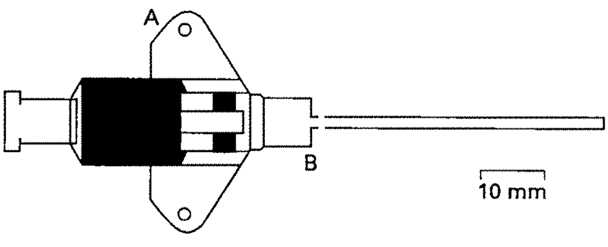

Figure 1 Ohmeda arterial cannula with Flo Switch showing fenestrated plate for suturing (A) and point of severance by cutting needle (B).

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The patient made a rapid and uneventful recovery from both operations with normal hand function when assessed 2 and 5 weeks after operation.

Discussion

Continuous display of arterial pressure[1] by cannulation of an accessible artery is a valuable adjunct in the management of complex and difficult surgical cases, and during respiratory support in intensive care. It is usual to cannulate the radial artery on the non-dominant side and, although minor complications are common, ischaemic injury is almost unknown[2-4]. The procedure appears to be safe when, in the absence of peripheral vascular disease, Allen's test[5] does not demonstrate adequate collateral circulation[6] or when failed radial cannulation is followed by cannulation of the ipsilateral ulnar artery[7].

The complications of arterial cannulation have been classified and comprehensively reviewed recently[8]. Immediate local complications are extravasation and haematoma formation: delayed local complications are reduced or absent flow, sensory impairment, infection, skin necrosis and false aneurysm. Distal complications include embolization of the deep palmar arch by thrombus from the wall of a partially occluded vessel, from the external surface of the cannula or flushed from the lumen of the device. The extensive interconnections between the palmar arterial arches and their many branches appear to be highly protective of circulation to the digits: minor embolic events are not clinically obvious and their incidence is unknown. Partial or complete radial artery occlusion, which occurs in approximately 25% of cannulations and is more common in women and after haematoma formation[7], is almost invariably devoid of clinical signs.

Foreign bodies in peripheral arteries are rare and result from missile injuries[9 10], radiological interventions[11] or complications of surgery[12 13]. There has been one report of palmar arch embolization from a penetrating injury of the forearm[14] and none from arterial catheter fragments. The concern in the last case quoted, as in this, was that distal embolization might lead to digital ischaemia or later infection with the attendant risk of secondary haemorrhage or mycotic aneurysm formation.

Management of foreign body emboli which have been investigated fully and are causing no problems, or which are difficult to deliver, may be conservative[14 15] but most agree that the foreign body should be localized by radiological and angiographic studies and retrieved if possible.

Small peripheral arteries are presently beyond the reach of interventional radiology[15] and therefore retrieval implies surgery. In our case there was no immediate circulatory compromise, a limited and accessible field for exploration (even under local anaesthesia) and surgical skills and equipment were available. Somewhat surprisingly exploration of the deep palmar arch by embolectomy catheter was fruitless and the 43-mm long fragment was delivered subsequently from the arterial lumen proximal to the arteriotomy. Without radiological studies the reasons for its immobilization are conjectural: impaction in the vessel wall and local spasm[11] may have contributed, as may the length and relative rigidity of the fragment in what was probably a small and tortuous artery.

The lessons of the episode are clear: first, when fixing arterial cannulae, suture needles should be kept well clear of the devices; second, when distal exploration for an arterial foreign body is fruitless, proximal exploration may be worthwhile before resorting to imaging studies.

References

1. Zorab JSM. Continuous display of the arterial pressure. *Anaesthesia* 1969; **24**: 431–437.
2. Bedford RF, Wollman H. Complications of percutaneous radial-artery cannulation: an objective prospective study in man. *Anesthesiology* 1973; **38**: 228–236.
3. Gardner RM, Schwarz R, Wong HC, Burke JP. Percutaneous indwelling radial-artery catheters for monitoring cardiovascular function. *New England Journal of Medicine* 1974; **290**: 1227–1231.
4. Evans PJD, Kerr JH. Arterial occlusion after cannulation. *British Medical Journal* 1975; **3**: 197–199.
5. Allen EV. Thromboangiitis obliterans: methods of diagnosing chronic occlusive arterial lesions distal to the wrist with illustrative cases. *American Journal of Medical Science* 1929; **178**: 237–244.
6. Wilkins RG. Radial artery cannulation and ischaemic damage: a review. *Anaesthesia* 1985; **40**: 896–899.
7. Slogoff S, Keats AS, Arlund C. On the safety of radial artery cannulation. *Anesthesiology* 1983; **59**: 42–47.
8. Hutton P. Complications of arterial cannulation. In: Hutton P, Prys-Roberts C, eds. *Monitoring in Anaesthesia and Intensive Care*. London: Saunders, 1994; 134–138.
9. Massad M, Slim MS. Intravascular missile embolisation in childhood: report of a case, literature review and recommendations for management. *Journal of Pediatric Surgery* 1990; **25**: 1292–1294.
10. Kuroiwa T, Tanabe H, Ogawa D, Ohta T. Traumatic intracranial foreign body embolisation—case report. *Neurologia Medico-Chirurgica* 1994; **34**: 810–813.
11. Egglin TKP, Dickey KW, Rosenblatt M, Pollack JS. Retrieval of intravascular foreign bodies: experience in 32 cases. *American Journal of Radiology* 1995; **164**: 1259–1264.
12. North K, Kan A, de Silva M, Ouvrier R. Hemiplegia due to posterior cerebral artery occlusion. *Stroke* 1993; **24**: 1759–1760.
13. Cina SJ, Raso DS, Crymes LW, Upshur JK. Fatal suture embolism of the left anterior descending coronary artery. A case report and review of the literature. *American Journal of Forensic Medicine and Pathology* 1994; **15**: 142–145.
14. Bentz M, Jones NF. Foreign body arterial embolus to the hand. *Journal of Hand Surgery* 1992; **17A**: 484–486.
15. Cantarelli MJ, de Paola A de A, Alves CM, Souza JA, Castello Junior HJ, Hermann JL, Lamounier EN, Guimaraes RF, Portugal OP, Martinez Filho EE. Percutaneous retrieval of intravascular foreign bodies (in Portuguese). *Arquivos Brasileiros de Cardiologia* 1993; **60**: 171–175.

British Journal of Anaesthesia 1996;77:432–434

EQUIPMENT

An effective method of scavenging nitric oxide

S. Squire, R. Kightley and A. J. Petros

Summary

We report an effective method of scavenging nitric oxide and nitrogen dioxide. We have compared three agents, a commercially available filter, soda lime and activated charcoal, for their effectiveness and duration of action. Complete absorption of nitric oxide and nitrogen dioxide for a period of 170 h was obtained using the commercial filter. However, soda lime and charcoal were unable to successfully scavenge either gas. The resistance characteristics of this filter when dry or humidified were determined. (*Br. J. Anaesth.* 1996;**77**:432–434)

Key words

Gases non-anaesthetic, nitric oxide. Gases non-anaesthetic, nitrogen dioxide. Equipment, filters.

Inhaled nitric oxide can significantly improve oxygenation in both paediatric[1 2] and adult populations[3] and it is invaluable in the treatment of critically ill patients. Effective scavenging of this gas and its higher oxides may present an obstacle for those wishing to take advantage of this new treatment. Various groups of health care workers looking after patients receiving inhaled nitric oxide have expressed concern over long-term exposure. Many individuals can detect a bitter odour when working with nitric oxide, even at very low concentrations. However, having undertaken a risk assessment, advice from NHS Estates (personal communication, Mr L. W. M. Arrowsmith, Chief Engineer, NHS Estates, Trevelyan Square, Leeds) is that provided there is adequate ventilation, scavenging is not necessary. Despite this reassurance we have continued to search for an effective method of scavenging nitric oxide exhaust. Foubert and colleagues[4] have demonstrated convincingly the limited role of soda lime during administration of nitric oxide, and others have shown that simple activated charcoal is also ineffective[4–6]. We have found a device available from the chemical industry and have compared it with soda lime and activated charcoal.

Methods

The Evita 2 (Draeger, Hemel Hempstead) ventilator was used under normal clinical conditions with a peak inspiratory flow of 60 litre min^{-1}, frequency of 12 bpm, tidal volume of 0.5 litre, minute volume of 6.1 litre min^{-1} and 100% oxygen to maximize nitrogen dioxide production. Positive end-expiratory pressure (PEEP) was not used.

We compared the absorbance characteristics of 1 kg of soda lime (Draeger-sorb, PN 6750701, Hemel Hempstead) in a scavenging canister (East Health Care, Littlemore, Oxford), activated charcoal (Carbomix, Penn Pharmaceuticals, Gwent) in a 300-mm length of 22-mm corrugated ventilator tubing (Intersurgical, Berkshire) and a commercially available filter, ABEK HgCONO-P3 (No. 67-35-813, Drager Industrial Ltd, Kilty Brewster Industrial Estate, Blyth, Northumberland), used in industry to absorb nitric oxide and nitrogen dioxide (fig. 1).

Over a continuous 170-h period, 1% nitric oxide in nitrogen (BOC, Special Gases, Guildford) was introduced into the ventilator circuit containing the ABEK filter (fig. 2) at a flow rate of 0.05 litre min^{-1}. The resultant nitric oxide and nitrogen dioxide concentrations were monitored proximal and distal to the ABEK filter with an electrochemical detector (Micromedical, Kent) at increasing intervals for a total of 170 h continuously. The monitors were calibrated using Spectraseal calibration gases (BOC, Special Gases, Guildford), nitric oxide in nitrogen at 86.1 ppm and nitrogen dioxide in air at 17.6 ppm. The proximal nitric oxide concentration was maintained between 55 and 70 ppm producing nitrogen dioxide concentration between 9 and 12 ppm.

Using the same conditions and experimental design, the 1-kg canister of soda lime and a 300-mm length of 22-mm corrugated tube containing activated charcoal were tested for absorbance. The tests

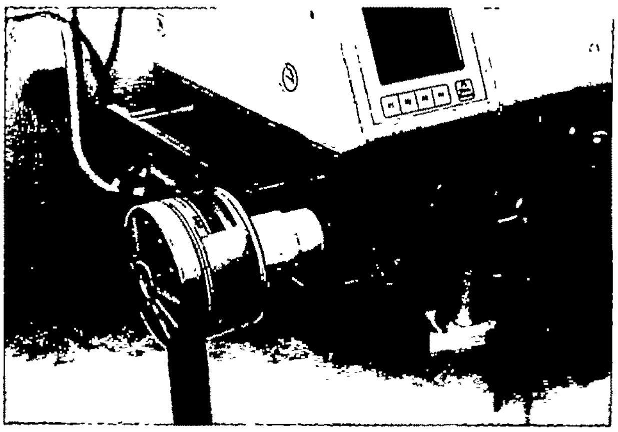

Figure 1 The ABEK HgCONO-P3 filter.

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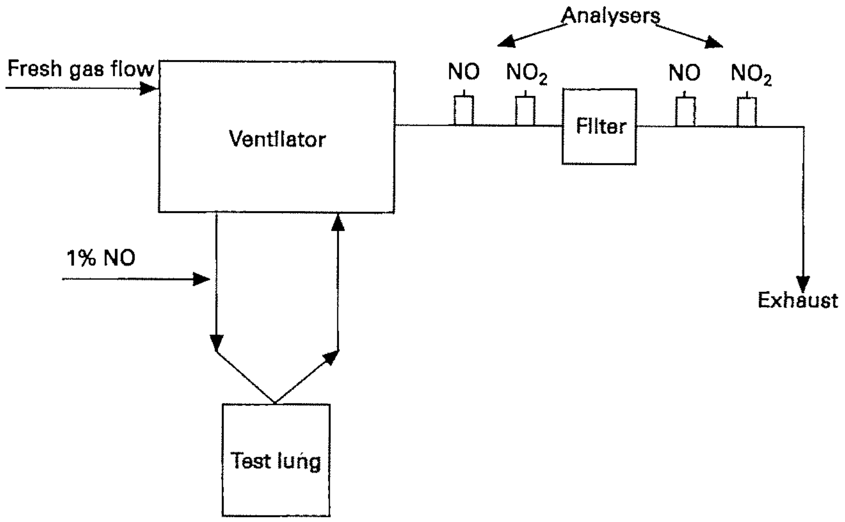

Figure 2 Circuit design for administering and measuring nitric oxide and nitrogen dioxide, and testing the degree of absorption.

were aborted when no absorption was apparent for either soda lime or charcoal.

In a separate series of experiments, the pressure created by fresh gas flows of 10–120 litre min^{-1} through the ABEK HgCONO-P3 filter were measured using a pressure meter (Druck, DPI 701, Druck Ltd, Leicester). Humidified gas at 37 °C and 80% humidity was passed at 19 litre h^{-1} through the filter for 35 h (1.5 litre of water was consumed) making the filter wet, and the expiratory pressures created by the filter at various flows were measured again. Humidity was measured with a relative humidity meter (Vaisala HM34, Cambridge) with an accuracy of ±3%.

Results

With a fresh gas flow of 9.0 litre min^{-1}, the calibration gas of nitric oxide in nitrogen at 86.1 ppm was passed through the soda lime canister and the concentration in the exhaust decreased to a low of 75 ppm, but for only 1 min. After 3 min the concentration had returned to 83 ppm and after 10 min there was no absorption. The test was repeated with a calibration gas of 17.6 ppm of nitrogen dioxide in nitrogen (BOC, Guilford). By 16 min, 14.6 ppm of nitrogen dioxide were detected distal to the soda lime canister. These tests were repeated using activated charcoal and no reduction in exhaust gas concentration was detected at any time.

Using the ABEK HgCONO-P3, we were able to completely scavenge both nitric oxide and nitrogen dioxide from levels of 55–70 ppm and 9–12 ppm, respectively, to less than 0.4 ppm for both gases for a continuous period of 170 h. By multiplying nitric oxide/nitrogen dioxide concentrations by the time intervals between readings, the volume of nitric oxide absorbed over this 170-h period was estimated to be 3.92 litre, and 0.67 litre for nitrogen dioxide.

The ABEK filter produced a linear increase in pressure with increasing flow rate when both dry and wet; when dry, resistance was 0.086 kPa litre min^{-1}; when wet, having been humidified for 35 h, resistance was 0.091 kPa litre min^{-1} (fig. 3). At 10 litre min^{-1}, the pressure generated within the test circuit was 0.1 kPa and at 60 litre min^{-1} 0.45 kPa.

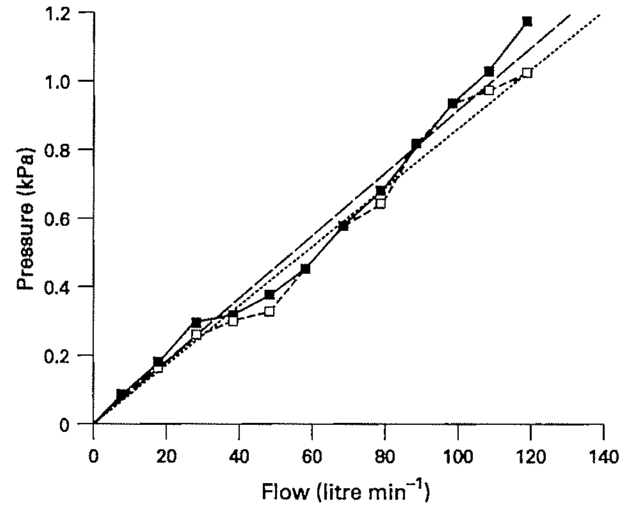

Figure 3 Pressures created by various flow rates through the filter were measured. Humidified gas at 37 °C and 80% humidity was passed through the filter for 35 h (a total of 1.5 litre of water) and the pressure at various flows measured again. The resistance of the filter when dry (□) was calculated to be 0.086 kPa litre^{-1} min^{-1} and when wet (■) 0.091 kPa litre^{-1} min^{-1}. (Regression coefficient, r^2=0.98 for both curves.)

Discussion

Current recommendations state that in a well ventilated environment, administration of nitric oxide poses no health hazard and that scavenging is not necessary. However, there are situations where nitric oxide may be delivered in less than ideal circumstances; in ambulances during transport of neonates; in a catheter laboratory; and in isolation cubicles with inadequate ventilation. For these situations scavenging of nitric oxide is desirable.

We have tested three methods and have found a commercially available filter which removes all nitric oxide and nitrogen dioxide. We can also support previous reports that soda lime and charcoal are of little value. The initial reduction in nitric oxide concentration we observed in the first minute of exposure to soda lime may have been caused by oxidation of nitric oxide to nitrogen dioxide by residual oxygen in the absorber rather than true absorption. Alternatively, the indicator dye within the soda lime may be independently involved in scavenging[4–6]. Charcoal from organic sources, for example coconut, can be activated by heating to high temperatures to create absorptive pockets of varying size on the charcoal particles. Larger molecules are removed more easily, ethanol being at the lower limit of effective removal and smaller molecules such as nitric oxide are not effectively scavenged.

We found the ABEK HgCONO-P3 filter the most effective method of scavenging nitric oxide and nitrogen dioxide. The ABEK HgCONO-P3 filter contains microglass fibres coated with copper and chromium salts. The filter also contains manganese dioxide and copper oxide as catalysts. Scavenging nitric oxide itself is difficult; it is much easier to scavenge nitrogen dioxide. The filter oxidizes nitric oxide to nitrogen dioxide which may then be absorbed by the copper and chromium salts.

$$2NO+O_2 \rightarrow 2NO_2$$

$$2NO_2+H_2O \rightarrow HNO_3+HNO_2$$

$$2HNO_3+CuX/CrX \rightarrow Cu(NO_3)/Cr(NO_3)+H_2O$$

It is estimated by the manufacturers that the filter can take up to 4–5 litre of nitric oxide and nitrogen dioxide in total, at a flow rate of 8 litre min^{-1}.

All our ventilators, Evita 1 and Evita 2 (Draeger Medical, Hemel Hempstead, Herts) Servo 900c (Siemens, Bracknell, Berkshire) and Brompton Manley (Porton, Denmark) are now fitted with the filter on the expiratory port whenever nitric oxide is used. The extra expiratory resistance introduced of approximately 0.01 kPa $litre^{-1}$ min^{-1} or 0.6 kPa at 60 litre min^{-1} is an acceptable level for the advantage of complete removal of nitric oxide and nitrogen dioxide from the environment. Although the filter lasts for up to 170 h we change it every 96 h. The current price is approximately £20.00.

Having performed a risk analysis, the recommendation of the NHS Estates is that scavenging is not necessary in an adequately ventilated environment (personal communication, Mr L. W. M. Arrowsmith, Chief Engineer, NHS Estates). This view is supported by other clinical reports where nitric oxide has been found to be negligible in the environment during inhaled treatment[4]. However, by using the ABEK filter we are guaranteed a nitric oxide free environment. Although we accept that exposure to nitric oxide in a well ventilated area may carry no significant risk, we suggest the use of the ABEK filter on the expiratory exhaust limb of ventilators when delivering nitric oxide to further reassure all those working with nitric oxide.

References

1. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; **340**: 818–819.
2. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalation nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; **340**: 819–821.
3. Rossaint F, Falke KJ, Laoez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328**: 399–405.
4. Foubert L, Mareels K, Latimer R, Herregods L, Rolly G. Limited role of soda lime during the administration of inhaled nitric oxide. *British Journal of Anaesthesia* 1995; 74: (Suppl. 1); A403.
5. Stenqvist O, Kjelltoft B, Lundin S. Evaluation of a new system for ventilatory administration of nitric oxide. *Acta Anaesthesiologica Scandinavica* 1993; 37: 687–691.
6. Pickett JA, Moors AH, Latimer RD, Mahmood N, Ghosh S, Oduro A. The role of soda lime during administration of inhaled nitric oxide. *British Journal of Anaesthesia* 1994; 72: 683–685.

British Journal of Anaesthesia 1996;77:435–437

CORRESPONDENCE

The care of patients and transport by air

Sir,—I read with great interest the recent review on pre-hospital monitoring of trauma patients[1]. This raised many important issues which need to be addressed further as expectations of out of hospital care increase. In Scotland there has been a fully integrated air ambulance service following a major reorganization in 1993. In addition to providing a primary patient transport service, there are also a large number of secondary inter-hospital transfers. Because of the distances involved and terrain, many of these involve air travel, using fixed-wing or rotary aircraft. In addition to adopting the Association of Anaesthetists' guidelines on minimum standards of monitoring, it has also been suggested that the recommendations for assistance should be followed in such situations[2].

Dr Morley highlighted in his review that monitoring can interfere with aircraft electrical systems. Most monitors give out a small amount of electrical activity to the surroundings; this is not true of defibrillators which, despite having been used successfully in-flight, still pose a greater hazard. It is recommended that authority is gained from the aircraft captain before defibrillators are discharged when airborne[3].

In addition to the function of monitors in the air environment, associated alarm systems have also come under scrutiny. The noise levels present in the back of an aircraft can render auditory alarms ineffective. It has also been demonstrated that relying on visual scanning for detection of problems leads to delays before alarm conditions are detected. Consideration is currently being given to incorporation of alarms into intercom systems to further increase safe practice[4].

All adverse events are more likely with prolonged journey times. With the move to centralize specialist facilities and notably paediatric intensive care units[5], patient transfer requiring sophisticated monitoring is set to increase. Only by continued vigilance and debate will standards improve to keep pace with these developments.

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1. Morley AP. Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service. *British Journal of Anaesthesia* 1996; 76: 726–730.
2. Oakley PA. The need for standards in interhospital transfer. *Anaesthesia* 1994; 49: 565–566.
3. Colvin AP. The use of defibrillators in helicopters. *Journal of the British Association of Immediate Care* 1992; 15: 35–37.
4. Fromm RE, Campbell RN, Schlieter P. Inadequacy of visual alarms in helicopter air medical transport. *Aviation, Space and Environmental Medicine* 1995; 66: 784–786.
5. Dryden CM, Morton NS. A survey of interhospital transport of the critically ill child in the United Kingdom. *Pediatric Anesthesia* 1995; 5: 157–160.

Sir,—Dr Shirley raises some interesting points which merit further comment. HEMS was certainly preceded by some air ambulance services in the UK, although it differs in several important respects. Most obvious of these is the presence of a full-time medical staff, trained specifically for the purpose of primary retrieval by helicopter of major trauma victims. It is difficult to exclude other factors when considering the specific added effect of a physician on an aeromedical prehospital team. One American study of blunt trauma patients found that patient mortality was 35% less than predicted by trauma score and injury severity score (TRISS) methodology when the attending aeromedical team incorporated a doctor. In addition, mortality in this group was significantly lower than in a group of patients, with similar TRISS scores, attended by a flight nurse/flight paramedic team. The doctors were able to perform a wider range of practical procedures than their paramedical counterparts, including thoracostomy, cricothyroidotomy and pericardiocentesis[1].

On the issue of defibrillators, HEMS use the Lifepak LP10-23 (Physio-Control Corporation International, Redmond, WA, USA), which is specifically approved by the Civil Aviation Authority for the HEMS aircraft, an Aerospatiale Dauphin SA 365N. The defibrillator monitoring unit initially caused low level interference in the 120-MHz radio frequency band and this has been resolved by special modifications. Similar problems have been encountered on testing the Lifepak LP10-59 in the Bölkow 105DBS used by Cornish First Air (personal communication, R. Dawnay, Snaefell Aviation Design). Interestingly, in-flight defibrillation can only be heard as a faint click on the aircraft headsets.

Since HEMS began operations in 1989, only 18 patients have undergone defibrillation. In most instances, the defibrillator was used on scene, not in the aircraft. The three survivors had all crashed their cars after sustaining cardiac arrests while driving and their injuries were only minor. The dismal prognosis of genuine traumatic cardiac arrest has been reported elsewhere[2].

Auditory monitor alarms are ineffective in the HEMS Dauphin. All staff on board wear helmets. Noise levels in the aircraft are very high because of removal of the soundproofing that normally forms part of the shell of the helicopter. This modification helped to lighten the aircraft, thereby improving performance and increasing potential patient load. Staff can communicate using helmet-based headsets and microphones. To avoid unnecessary disturbance to the pilot, incorporation of any alarm system into the intercom would have to be restricted to the headsets of the doctor and paramedic.

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1. Baxt WG, Moody P. The impact of a physician as part of the aeromedical prehospital team in patients with blunt trauma. *Journal of the American Medical Association* 1987; 257: 3246–3250.
2. Rosenmurgy AS, Norris PA, Olson SM, Hurst MD, Albrink MH. Prehospital traumatic cardiac arrest: the cost of futility. *Journal of Trauma* 1993; 35: 468–473.

Effect of naloxone on nitrous oxide analgesia

Sir,—We would like to comment on the article by Yagi and colleagues[1]. These authors were unable to show naloxone inhibition of the analgesic effects of nitrous oxide when measurements of analgesia were obtained 5 min after injection of naloxone. In fact, in figure 3 they showed a non-significant increase in analgesia after administration of naloxone[1]. Interestingly, these authors used very low doses of naloxone. We have shown previously that with similar doses of naloxone in human volunteers, the peak effect of naloxone was measurable only within the first 2–3 min after bolus injection. This effect was not apparent after 5 min[2,3]. Although in a minority of subjects nitrous oxide analgesia was attenuated by naloxone[2] the majority of subjects showed a transient increase in nitrous oxide analgesia[2,3]. These observations were confirmed later by others in animals[4]. From our findings we proposed the existence of two opioid systems, in dynamic equilibrium: one analgesic and the other pain producing[2,3].

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1. Yagi M, Mashimo T, Kawaguchi T, Yoshia I. Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *British Journal of Anaesthesia* 1995; 74: 670–673.
2. Gillman MA, Kok L, Lichtigfeld FJ. Paradoxical effect of naloxone on nitrous oxide analgesia in man. *European Journal of Pharmacology* 1980; 61:175–177.
3. Gillman MA, Lichtigfeld FJ. Nitrous oxide analgesia is potentiated by low doses of naloxone: more possible evidence for a hyperalgesic opioid system. *South African Journal of Science* 1987; 83: 560–563.
4. Quock RM, Curtis BA, Reynolds BJ, Mueller JL. Dose-dependent antagonism and potentiation of nitrous oxide antinociception by naloxone in mice. *Journal of Pharmacology and Experimental Therapy* 1993; 267: 117–122.

Sir,–In a previous article[1] we reported that the clinical dose of naloxone did not antagonize the analgesic action of nitrous oxide when the pain threshold test was performed 5 min after injection of naloxone in humans. As Gillman and Lichtigfeld pointed out, the dose (0.01 mg kg^{-1}) of naloxone used in the study may not have been adequate to fully antagonize the effects of the opioid[2]. We chose this dose according to Jaffe and Martin[3] who indicated that naloxone 0.4–0.8 mg i.v. in humans can prevent or reverse the effects of mu opioid agonists. The onset of action of naloxone is fast and seen within 1 or 2 min after injection[3,4]. The duration of antagonistic effects is approximately 45 min after an i.v. dose of 0.4 mg[5]. In our previous study, measurement of pain threshold was commenced 5 min after administration of naloxone. Measurement of analgesia was obtained during the period of naloxone-induced antagonism. We also evaluated antagonism of nitrous oxide analgesia with higher doses (5 and 10 mg kg^{-1}) of naloxone by a radiant heat tail-flick test in rats (unpublished data). The results indicated that naloxone did not antagonize the analgesic action induced by nitrous oxide, even at high doses.

Gillman, Kok and Lichtigfeld[6] showed that the peak effect of naloxone was measurable only within the first 2–3 min after bolus injection with clinical doses of naloxone in human volunteers, but not after 5 min. The majority of subjects showed a transient increase in nitrous oxide analgesia. This interesting peak effect of naloxone might be an agonistic effect seen at high doses of naloxone. Naloxone enters the brain very rapidly. The initial brain concentration of naloxone was reported to be much higher (4.6 times) than that in serum[4]. Therefore, the brain concentration of naloxone may transiently reach a high level which may produce agonist effects during the short period after bolus injection of clinical doses. High doses of naloxone produce increased arterial pressure and arrhythmias which may be caused by the release of sudden intense sympathetic activity. Enhancement of sympathetic neurones by naloxone in the central nervous system may explain the transient increase in nitrous oxide analgesia 2–3 min after injection of naloxone.

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1. Yagi M, Mashimo T, Kawaguchi T, Yoshiya I. Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *British Journal of Anaesthesia* 1995; **74**: 670–673.
2. Yaksh TL, Howe JR. Opiate receptors and their definition by antagonists. *Anesthesiology* 1982; **56**: 246–249.
3. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *The Pharmacological Basis of Therapeutics*, 8th Edn. Oxford: Pergamon Press, 1990; 485–521.
4. Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector S. Pharmacokinetics of naloxone in rats and in man: Basis for its potency and short duration of action. *Anesthesiology* 1976; **44**: 398–401.
5. Evans JM, Hogg MIJ, Lunn JN. Degree and duration of reversal by naloxone of effects of morphine in conscious subjects. *British Medical Journal* 1974; **1**: 589–591.
6. Gillman MA, Kok L, Lichtigfeld FJ. Nitrous oxide analgesia is potentiated by low doses of naloxone: more possible evidence for a hyperalgesic opioid system. *European Journal of Pharmacology* 1980; **61**: 175–177.

Difficult tracheal intubation

Sir,—Difficult tracheal intubation is a major cause of anaesthetic-related morbidity and mortality, and any change which may lead to a reduction is to be welcomed. However, we were interested that when West and colleagues studied a tracheal tube designed specifically for this reason, they used a size 8 tube for females and size 9 for males[1]. While we know of no firm evidence that decreasing the size of the tracheal tube facilitates intubation in cases of difficulty, it does seem to be true in both our experience and that of others[2]. Furthermore, it has been known for many years that small tracheal tubes can be used safely and without complication during positive pressure ventilation[2]. It has become routine practice at this institution to use 6-mm tubes in females and 6.5-mm in males. We believe that West and colleagues would have found an increased success rate and shortened learning time had they used smaller tracheal tubes in their simulation of a difficult intubation.

The authors' incidence of 33% for sore throat is similar to that quoted in other studies[3], but 1–3% of patients may still have hoarseness up to 6 months after intubation[4]. This value may be expected to be even higher in cases of difficult intubation where greater degrees of laryngeal trauma are likely to occur[3]. We believe that decreasing the size of the tracheal tube makes intubation easier and reduces the incidence of laryngeal damage. Stout and coworkers[5] have shown that the incidence of hoarseness and sore throat may be reduced substantially by using tracheal tubes of size 7 or less. We believe that small tracheal tubes can be used routinely, and should be used when laryngoscopy is difficult.

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1. West MRJ, Jonas MM, Adams AP, Carli F. A new tracheal tube for difficult intubation. *British Journal of Anaesthesia* 1996; **76**: 673–679.
2. Stenqvist O, Sonander H, Nilsson K. Small endotracheal tubes. Ventilator and intratracheal pressures during controlled ventilation. *British Journal of Anaesthesia* 1979; **51**: 375–380.
3. Jones MW, Calting S, Green DH, Green JR. Hoarseness after tracheal intubation. *Anaesthesia* 1992; **47**: 213–216.
4. Kambic V, Radsel Z. Intubation lesions of the larynx. *British Journal of Anaesthesia* 1978; **50**: 587–589.
5. Stout DM, Bishop MJ, Dwersteg JF, Cullen FC. Correlation of endotracheal tube size with sore throat and hoarseness after general anesthesia. *Anesthesiology* 1987; **67**: 419–421.

Sir,—Our thanks to Drs Broomhead and Vaughan for their comments. The crucial step is to get the introducer into the right hole; when that is achieved, intubation with our tube is easy; that is its main advantage. It seems unlikely that smaller tubes would have altered the intubation time. With a Magill tube, when the introducer is in place, there is still the problem of preventing the bevel snagging on the cords and a smaller tube is often helpful, but with the new method a smaller tube is needed only if the larynx is abnormally small. The problem is simplified because instead of two possible causes of resistance, there is only one. Occasionally, some resistance is felt and a smaller tube is needed. Recent data[1] suggest that over the past decade the incidence of failed intubation in obstetrics has increased. The authors imply that part of the explanation is that junior staff have less experience of obstetric general anaesthesia than in the past. If that is correct then it underlines our conclusions.

On the other hand, routine use of a small tube implies that there is never any need to change tubes, which is perhaps an advantage. The authors also refer to Stout and colleagues[2] who found that with size 7 tubes the incidence of sore throat was 22% compared with 33% in our study. But this could be fortuitous (P=0.1); a larger sample might show a real difference. Thus the case for smaller tubes is not proved but we agree that it merits further study.

May we add that the most serious cause of trauma is the novice who attempts to handle difficult intubations with no clear picture of the problem or its solution. This is perhaps the strongest argument in favour of our training drill.

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1. Hawthorne L, Wilson R, Lyons G, Dresner R. Failed intubation revisited: 17 yr-experience in a teaching maternity unit. *British Journal of Anaesthesia* 1996; **76**: 680–684.

2. Stout DM, Bishop MJ, Dwersteg JF, Cullen FC. Correlation of endotracheal tube size with sore throat and hoarseness after general anesthesia. *Anesthesiology* 1987; 67: 419–421.

Cost of volatile anaesthetic agents

Sir,—I read with interest Dr Barker's letter on the cost of volatile anaesthetic agents[1]. When the costs of various agents are listed, one is tempted to make comparisons, and economic concerns are of increasing importance in our practice. However, for fair comparison of the available agents, we need to consider the amount of anaesthetic required to provide a similar depth of anaesthesia and this extends beyond making comparisons of similar potencies at set fresh gas flow rates. Differences in solubility of various agents in the blood and tissues become important. The amount of anaesthetic agent required may be divided into that required to provide adequate anaesthesia at the start (to load up the circuit and the patient's lungs), to that required to replace anaesthetic taken up into the blood and then into the tissues of the body, and also make account of that supplied in excess of uptake and therefore lost from the circuit and wasted. The relative cost of the available agents varies with the fresh gas flow chosen.

Estimates have been made of the volume of liquid anaesthetic required based on uptake kinetics and circuit performance at various fresh gas flow rates to sustain an alveolar concentration of 1 MAC for four of the volatile agents listed by Dr Barker[2]. I have included the price per millilitre of liquid anaesthetic, from the British National Formulary[3], to calculate the cost of the volatile agent required (table 1).

There are limitations to the calculations: at low fresh gas flows, conventional vaporizers may be unable to supply sufficient agent, for example at 0.2 litre min^{-1} at 1 MAC, isoflurane vaporizers cannot supply a sufficient amount of isoflurane for the first hour, whereas desflurane vaporizers are unable to do so for the first 10 min. The increased fresh gas flow required to compensate for the limitations of the vaporizers would increase the estimated cost noted in table 1, but this would be greatest for the more soluble volatile agents. In addition, there is some concern on the use of sevoflurane at low fresh gas flows[4]. Table 1 shows, as would be expected, that for any given volatile agent, cost increases with increased fresh gas flow, but also that the relative cost of the less soluble (and newer) volatile agents is reduced at lower fresh gas flows. This illustrates that when comparing the costs of volatile anaesthetic agents, consideration must also be given to uptake kinetics and fresh gas flows used.

Table 1 Cost of volatile agent required to maintain an alveolar concentration of 1 MAC, of the chosen volatile agent, at various fresh gas flow rates, for periods of 30 or 60 min

	Fresh gas flow rate (litre min^{-1})				
	0.2	1	2	4	6
Halothane					
30 min	£0.13	£0.17	£0.23	£0.34	£0.45
60 min	£0.20	£0.28	£0.38	£0.59	£0.80
Isoflurane					
30 min	£1.56	£2.26	£3.12	£4.80	£6.51
60 min	£2.46	£3.74	£5.42	£8.70	£11.97
Sevoflurane					
30 min	£1.62	£3.10	£4.97	£8.66	£12.40
60 min	£2.41	£5.36	£8.95	£16.24	£23.52
Desflurane					
30 min	£1.30	£2.87	£4.84	£8.76	£12.67
60 min	£1.96	£5.06	£8.91	£16.62	£24.35

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1. Barker I. Cost of volatile agents. *British Journal of Anaesthesia* 1996; 76: 749.
2. Eger EI II. Uptake and distribution. In: Miller RD, ed. *Anesthesia*, 4th Edn. New York: Churchill Livingston, 1994; 101–123.
3. *British National Formulary*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1996; 518–519.
4. Eger EI II, Martin JL, Tinker JH. The safety of sevoflurane has not been adequately established. *Anesthesia and Analgesia* 1996; 82: 431–432.

ERRATUM

British Journal of Anaesthesia 1996; **76** (Suppl. 2): A.45

In the methods section of this abstract, the dose of morphine was reported incorrectly: morphine 0.9 mg/kg should read *morphine 0.09 mg/kg*.

We apologize to the authors for this confusion.

British Journal of Anaesthesia 1996;77:438–439

BOOK REVIEWS

Clinical Orthopedic Anesthesia. J. E. TETZLAFF. Published by Butterworth-Heinemann, Massachusetts. Pp. 406; indexed; illustrated. Price £45.00.

This book is intended for the trainee approaching a subspecialty attachment in orthopaedic anaesthesia and is produced in a notebook sized format with a ring binding to make it easy to use in the operating theatre. It is an attractive format but I hope that the binding is more durable than that of my road atlas.

Dr Tetzlaff has written all of the 22 chapters with the assistance of four contributors, and all are based at the Cleveland Clinic. There is therefore a consistency of style which makes a welcome change from multi-authored texts so that the book is easy and enjoyable to read. The authority of the text is derived from Dr Tetzlaff's clear experience of orthopaedic anaesthesia and his personal view of clinical problems is welcome. The book represents US practice and British readers will find many differences from their own: most notably the complete absence of any reference to the use of the laryngeal mask airway.

Chapters 1 and 2 deal comprehensively with the preoperative preparation of patients for general and regional anaesthesia, respectively. The word "mandatory" is overworked and must give lawyers lots of ammunition, although the general stance of the book is very defensive: all chapters have comprehensive sections dealing with complications of the techniques discussed. While all systems are covered in these chapters, there is too little attention given to the special clinical problems of orthopaedic anaesthesia; thus muscular dystrophy and myopathies merit only one paragraph with no mention of cardiomyopathy and there are two paragraphs on haemophilia and sickle cell disease. The bone problems of end-stage renal failure and renal transplantation are omitted.

Chapter 3 is a long and very thorough description of positioning of patients, with heavy emphasis on complications, and is better suited to a general textbook of anaesthesia: there is little use of the lithotomy position in orthopaedic surgery. This chapter should have been followed by one on tourniquets which does not appear until chapter 14.

The next group of chapters are concerned with regional anaesthesia drugs and techniques. The chapter on pharmacology is long winded and much of the information on the drugs could have been summarized in a table. The complication of methaemoglobin formation with prilocaine is discussed but the effect on oximetry readings is omitted. Lignocaine is recommended for i.v. regional anaesthesia despite its well-known toxicity, which should preclude its use. A good section on spinal anaesthesia is followed by a word-processor error on page 117 where the treatment of hypotension caused by high spinal anaesthesia includes measures to *decrease* capacitance vessel tone.

The chapter on upper limb blocks is confident and interesting, and marred only by dislocation between text and illustrations, which is probably unavoidable in a small format book. The chapter on lower limb regional anaesthesia fails to discriminate between useful blocks and those of little relevance, such as obturator nerve block. The inclusion in occasional chapters of sections headed "controversy" is a good idea and adds to interest. The suggestion that continuous extradural anaesthesia prevents development of phantom limb pain after amputation could have been discussed.

Chapters 9 and 10 discuss anaesthesia for hip fracture and hip and knee replacement but this arrangement of information inevitably leads to much repetition from earlier chapters about spinal and extradural anaesthesia.

Chapter 11 is a very useful chapter on shoulder surgery, informed by a great deal of experience, such as how to drape the patient who is undergoing shoulder surgery under regional block. Spinal surgery is well described in chapter 12, with a good section on spinal cord monitoring. The order of chapters thereafter seems random, thus "Scoliosis" is not chapter 13 but 22 and chapters devoted to complications, "Deep venous thrombosis" and "Fat embolism" are 16 and 20.

The chapter on blood conservation, transfusion and coagulopathy (chapter 15) is interesting and important, with discussion of predonation of blood and cell salvage techniques, which are of growing importance in Britain. The chapter on paediatric orthopaedics (chapter 19) is too short and sketchy to be useful.

This book provides a good basis for a junior trainee about to embark on his first orthopaedic surgical list and the descriptions of surgical procedures are particularly good. Further reading is hampered as referencing is capricious and rarely up to date: the chapter on oncology has 23 references only one of which is in the last 10 yr. The book could have been more concise with less repetition if better cross referencing had been used and more use made of tables for comparative facts. Is it worth including references more than 10 yr old? There are some surprising omissions; the problems associated with extensive plasters and anaesthesia for replantation of severed parts, while anaesthesia for day surgery is dealt with feebly. Finally, the use of "anaesthesia providers" for "anaesthetists"" brings home the fact that the Health Service "reforms" grew out of US practice!

A. Loach

Clinical Anesthesiology, 2nd Edn. G. E. MORGAN JR AND M. S. MIKHAIL. Published by Appleton and Lange, Stamford, CT. Pp. 882; indexed; illustrated. $US45.

Some things are better avoided. You should never have to apologize for a "busy" slide. Nor should you tell audiences at lectures repeatedly that you do not have the time to cover everything. To these infelicities can be added that it is not a good idea to suggest to potential buyers of your book that there are already enough books on anaesthesia. Because there are: both in the UK and in the US markets, there are enough omnibus books on anaesthesia, at basic, intermediate and advanced levels, that the specialty would lose nothing if no new omnibus books appeared for 10 yr.

So I suggest that if Morgan and Mikhail attempt a third edition of their book they send out a new invitation for the foreword, which not only contains the sentence "Oh no, not another textbook of anesthesia!", complete with exclamation mark, but then gives the lead editors of three competitors.

Morgan and Mikhail have produced an attractive (if difficult to place) book covering the whole of anaesthesia in about 900 pages, including index. They have written the whole text, except for the two chapters on local and regional anaesthesia, covering the basic sciences, monitoring, legal matters and all of clinical anaesthesia. There are thus two pages on lung transplantation and a page on cardiac transplantation. This gives an insight into the American approach to disease and death: the opening sentence to the section on cardiac transplantation is that it is "the treatment of choice for patients with end-stage heart disease who are unlikely to survive the next 6–12 months." The only other comment on selection of patients for cardiac transplantation is that they should have no end-organ damage or other major systemic disease. This illustrates the strength and weakness of the book: it is comprehensive, but many sections are superficial. Hyoscine is described as "preventing motion sickness"; the anticholinergic drugs are described as mydriatics, with no distinction between systemic and topical use.

The book is difficult to place because there is not enough detail in the basic sciences for the primary FRCA, the clinical sections are too advanced for the primary FRCA, but are not detailed enough for the final FRCA. The American perspective is unhelpful if the book is used as a primer for British anaesthesia, although maybe this is realized: the price is given in dollars.

The book is well laid out, with contrasting blue type highlighting important points. The two-author approach makes for an easy style, but perhaps explains some statements that struck me as rather extreme. Should women having spinal anaesthesia for Caesarean section really receive 1500–2000 ml of Hartmann's solution before the onset of block? Is there really a risk of an allergic reaction to local anaesthetic used for skin infiltration before extradural injection? Treatment of a high spinal includes the advice to position the patient head down.

The new drugs are all there, although perfunctorily. There is a useful index of critical topics. Each chapter ends with a case discussion, some of which are imaginative enough that they must have happened, for example, the patient who died when an adrenaline infusion was labelled nitroglycerin. But there are no proper references, only reading lists, and it is almost lazy to give a reading list for cardiovascular physiology that consists of only other general textbooks.

The publishers advertise the book as suitable, in the American market, for medical students, residents, physicians and nurse anaesthetists. It has far too much for British medical students; our residents and physicians do not buy books on anaesthesia and the emphases are wrong for our anaesthetic nurses and ODAs. But there is a place for this book. Paradoxically, it is a reasonable book for someone who already has a good knowledge of anaesthesia, but wants an all-in-one book for occasional information, of the right size to fit in a briefcase. Until I buy a portable computer with a CD-ROM, and until I am as happy flicking through screens of text as I am flipping over the pages of a book, I suspect Morgan and Mikhail's *Clinical Anesthesiology* may do a bit of travelling with me.

N. W. Goodman

Baillière's Clinical Anaesthesiology: International Practice and Research, vol. 10, No. 1. The Lung in Anaesthesia and Intensive Care. R. G. Pearl (editor). Published by Baillière Tindall (W B Saunders Co Ltd), London. Pp. 236; indexed; illustrated. Price £30.

This volume is intended to contain reviews of recent advances in knowledge of the lung, which also show how these advances can affect patient care. A good review such as this is very difficult to write. The author needs to have extensive knowledge and even more importantly must provide a critical and balanced account so that the reader can obtain a coherent and intelligible view of the topic. The best example, close to this ideal, is the chapter by Pickworth and Jones on "Respiratory care", which is discursive, critical and wide-ranging. It covers topics such as respiratory secretions, oxygenation, physiotherapy and bronchodilators. Another useful contribution comes from Gal, on anaesthesia for patients with lung disease, covering the subject in a workman-like and clinically based way supported by good basic knowledge. Falke provides a first-class review of recent advances in the treatment of acute (no longer adult) respiratory distress syndrome, carefully avoiding unsubstantiated recommendations and indicating the many points where further study is required. In particular, he provides a good table of suggestions for treatment.

However, in this chapter and in others the editor could have helped by providing one of the principles of good aircraft design, which is to "simplify and add lightness". A chapter on the pulmonary circulation, which is truly a field of considerable recent advance, is fascinating but very closely packed and would have been much better expanded so that some of the important concepts could have been set out more fully. Here the clinical implications are not clearly indicated but perhaps we are still too close to the experimental information for this.

Unfortunately, to a greater or lesser extent, the remainder of the contributions do not meet the ideal. Hedenstierna, with the topic "Effects of anaesthesia on respiratory function", concentrates particularly on studies from his department on gas exchange and atelectasis, including the possible adverse effects of increased inspired oxygen fraction. The clinical relevance of these observations, and their exact relationship to postoperative complications, remain to be clarified. Other contributors to this volume have been set difficult tasks to cover vast subject areas and have not had the wisdom to limit their coverage. For example, mechanical ventilation for critical illness cannot be addressed easily in 23 pages, particularly if the first three are on history. To a lesser extent, the chapters on thoracic surgery and thoracic trauma are also cramped and limited, and are too general to be of clinical value. The chapter on respiratory monitoring is superficial and has some remarkable gaps, and the chapter on paediatric anaesthesia resembles a rushed examination answer with no light of clinical acumen visible, and no sign of a senior hand in the plan or execution.

In his preface, the guest editor suggests that large advances have taken place in the past 10 yr in the topics that are covered. A quick glance at the reference lists indicates that if this is true, it is not well reflected by some of the contributions, with one chapter having less than 30% of original references after 1986. More than 25% of the references for another chapter consist of references to standard textbooks.

In summary, only four of the 10 chapters meet my criteria of readability, topicality and sufficient critical thought. I would advise readers to look elsewhere, such as recent textbooks, for better coverage of the areas attempted by the other six chapters. Overall, the "topicality" of this book is limited and I would not buy it for myself, although I shall certainly go to my review copy for information on the pulmonary circulation and ARDS.

G. B. Drummond

Chemical Warfare Agents. Toxicology and Treatment. T. C. Marrs, R. L. Maynard and F. R. Sidell. Published by John Wiley and Sons, Chichester. Pp. 234; indexed. Price £40.00.

The use of chemical warfare agents is prohibited by several international treaties or conventions. Despite these prohibitions the number of countries who have acquired chemical weapons continues to increase. Regrettably there is a lack of sound moral or ethical compulsion to refrain from the use of such weapons and there is a continuing probability that chemical agents will be used in so called Third World conflicts. The very existence of these chemical weapons implies that they are likely to fall into the hands of terrorists and be used against civilian populations. Sarin has been used for such a purpose in recent years, in 1994 and 1995 in Japan, resulting in 15 deaths and hundreds of casualties.

This excellent book covers the toxicology of the commonest chemical warfare agents, including mechanisms of action, pathology and treatment of the resultant poisoning. Emphasis is placed on the more practical aspects of treatment and the particular difficulties of treatment in the field are not neglected. This book will be of interest to military medical officers and those practitioners engaged in civil defence planning. The chapters on organophosphate compounds will be of particular interest to anaesthetists.

The three authors of this book are experts in this field; two are British and the other is American. It was slightly irritating to find trans-Atlantic differences in spelling in the text. There are a total of 571 references in the 10 chapters of this book. Many of these references have not been in the public domain until recently and much of the work on these agents performed on human volunteers could not be repeated today. The authors are to be congratulated on the clarity of their style. The subject has been presented in a logical and easily readable format. There are no photographs but the text is illustrated by clear tables and figures.

The anaesthetist has the basic skills and resuscitative abilities to play an essential part in the treatment of chemical casualties. He or she should be involved in the training of paramedical staff, and the organization of civilian mass casualty disaster plans should include the mass toxic and mass traumatic catastrophes. This book is an excellent, authoritative source of information for such a purpose and good value for money.

J. Restall

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EDITORIAL

Ketamine: its mechanism(s) of action and unusual clinical uses

Since Domino, Chidiff and Corssen[1] reported the first clinical use of ketamine more than 30 yr ago, there have been many clinical and laboratory studies to determine both its mechanism(s) of action and define the most appropriate clinical use of this unusual anaesthetic agent. Although disturbing emergence reactions are associated with its use, ketamine has several clinically useful properties, including analgesia and less cardiorespiratory depressant effects than other anaesthetic agents, in fact it causes some stimulation of the cardiovascular system[1,2]. Clinically, ketamine has been reported to produce not only general but also local anaesthesia[3-5]. It also interacts with *N*-methyl-D-aspartate (NMDA) receptors[6-8], opioid receptors[9,10], monoaminergic receptors[11], muscarinic receptors[10,12,13] and voltage-sensitive Ca^{2+} channels[14,15]. However, unlike other general anaesthetic agents, ketamine does not interact with GABA receptors[16]. Clinically, ketamine is administered as a racemate composed of two optical isomers, S(+) and R(−), and there are some pharmacological differences between these[2] (see below).

In this editorial, in addition to the well established NMDA receptor inhibition, we review other potential pharmacological targets for ketamine and discuss the unusual clinical uses of this agent.

NMDA RECEPTOR ANTAGONISM

The NMDA receptor, a member of the glutamate receptor family, is an example of an ion channel-coupled receptor with excitatory properties[17] which has been implicated in the mechanism of general anaesthesia[16], analgesia[18] and also in neurotoxicity[7]. Ketamine is a non-competitive antagonist of the NMDA receptor Ca^{2+} channel pore[7]. In addition, at clinically relevant concentrations, ketamine interacts with the phencyclidine (PCP) binding site[9] leading to significant inhibition of NMDA receptor activity[8]; this occurs only when the channel has been opened[18]. This interaction with the PCP binding site appears to be stereoselective with affinity (K_i) values of 3.2 μmol litre^{-1} and 1.1 μmol litre^{-1} for S(+) and R(-) ketamine, respectively. An *in vivo* study in the lamprey eel[19] also showed that ketamine inhibits NMDA receptor-mediated neuronal events by 50% (IC_{50}) at 10–20 μmol litre^{-1}.

ANALGESIA AND INTERACTIONS WITH OPIOID RECEPTORS

Ketamine has been reported to interact with mu (μ), delta (δ) and kappa (κ) opioid receptors[10]. It has been shown *in vivo* that S(+)ketamine is 2–3 times more potent than R(-) ketamine as an analgesic[2]. In agreement with these clinical observations, it has been shown that ketamine produces 2–3 fold stereoselectivity at μ and κ receptors but not at δ receptors[10]. The interaction with opioid receptors is clearly complex and several studies[10,20] have suggested that ketamine may be an antagonist at μ receptors and an agonist at κ receptors. Smith and colleagues[20] found that morphine but not ketamine analgesia was antagonized by microinjection of naloxone into the periaqueductal grey (PAG) region of the rat brain, which contains μ but not κ receptors. Moreover, microinjection of ketamine into the PAG did not produce analgesia but antagonized the effects of morphine. These observations suggest that the analgesic effects of ketamine are not mediated via μ opioid receptors in the CNS. Clearly, further detailed studies with δ and κ agonists are required. While the σ receptor is no longer classified as an opioid receptor, ketamine also interacts with this receptor although the interaction is weak ($\mu > \kappa > \sigma > \delta$) and stereoselectivity is reversed: S(+)<R(−)[10].

ANALGESIA AND MONOAMINERGIC RECEPTORS

Crisp and colleagues found that ketamine (3.0 μmol litre^{-1})-induced spinal analgesia, measured as an increase in tail flick latency in rats, was reversed dose-dependently by administration of s.c. methysergide (serotonin antagonist), phentolamine (α-adrenoceptor antagonist) and naloxone (IC_{50} values 8.0 μg kg^{-1}, 0.88 mg kg^{-1} and 3.0 mg kg^{-1}, respectively)[11]. However, they also found that spinal ketamine did not increase tail-flick latency in rats with bilateral dorsal funiculus lesions (DFL) in a system where morphine was effective. These data suggest that the antinociceptive action of ketamine may involve descending inhibitory monoaminergic pain pathways. One possible flaw in this argument is that ketamine-sensitive opioid receptors on interneurones modulating descending antinociceptive pathways could not be excluded. Specifically, is the naloxone reversible action of ketamine secondary to its ability to interact with interneurones to block amine uptake, that is indirect?

LOCAL ANAESTHETIC ACTION

It is known that ketamine at high doses possesses local anaesthetic properties and these have been compared with lignocaine and procaine[3]. For example, spinal administration of 1.25% ketamine and lignocaine in dogs produced rapid, reversible and predictable segmental paralysis without any apparent reduction in consciousness[3]. In addition, ketamine and procaine inhibited, with identical IC_{50} values, the compound action potential of the frog sciatic nerve preparation[3]. In agreement with the mechanism of action of local anaesthetic agents, it has been shown that high-dose ketamine blocks Na^+ channels in frog neurones and in lipid bilayers (containing human Na^+ channels) with IC_{50} values in the mmol $litre^{-1}$ range[21 22]. Moreover, Durrani and colleagues reported that ketamine (>0.3%) produced adequate i.v. regional anaesthesia with complete sympathetic, sensory and motor block[5].

MUSCARINIC RECEPTORS

Ketamine anaesthesia is antagonized by anticholinesterase agents[12] which increase endogenous acetylcholine concentrations and there is evidence for an interaction of ketamine with muscarinic receptors[10 13]. Indeed, ketamine produced stereoselective interaction with muscarinic receptors in guineapig brain membranes in a series of binding experiments (K_i of S(+) and R(−)ketamine: 20 and 37 μmol $litre^{-1}$, respectively). In addition, Durieux[13] reported that clinically relevant concentrations of ketamine inhibited muscarinic signalling through M1 receptors expressed in *Xenopus* oocytes (IC_{50} 5.7 μmol $litre^{-1}$), the most prominent subtype in the cortex and hippocampus. Whether ketamine is an agonist or antagonist is unclear. However, as ketamine produces anticholinergic symptoms (postanaesthetic delirium, bronchodilatation and a sympathomimetic action) and ketamine anaesthesia is reversed by anticholinesterases, an antagonist action is likely.

VOLTAGE-SENSITIVE CA^{2+} CHANNELS (VSCC)

Interaction of ketamine with voltage-sensitive Ca^{2+} channels (VSCC) has not been studied extensively. Baum and Tecson[14] reported a small reduction (20%) in the peak current in guineapig myocardium with ketamine 10 and 100 μmol $litre^{-1}$. In addition, Yamakage, Hirshman and Croxton[15] reported that ketamine (>10 μmol $litre^{-1}$, IC_{50} 1 mmol $litre^{-1}$) significantly reduced the peak Ca^{2+} current in porcine tracheal smooth muscle cells. We have demonstrated previously, in cultured neuroblastoma cells, that ketamine produced non-competitive inhibition of K^+-stimulated increased intracellular Ca^{2+} (mediated by L channels), with an IC_{50} of 209 μmol $litre^{-1}$ [23]. The role of VSCC in the action of ketamine remains to be explored fully but non-competitive channel block (similar to the NMDA receptor) is possible.

Clinical use of ketamine

PAIN CONTROL

Systemic administration

Subanaesthetic doses of ketamine have been shown to be either potent analgesics[24] or ineffective[25] in the postoperative period. Recently, Arendt-Nielsen and colleagues[18] reported that a bolus of ketamine 0.5 mg kg^{-1} i.v. followed by continuous infusion at 9 μg kg^{-1} min^{-1} inhibited central temporal summation which is used as an index of dorsal horn responsiveness in humans. These authors demonstrated that ketamine could only inhibit NMDA receptor activity when the receptor-operated ion channel had been opened by nociceptive stimulation, and used this to explain why ketamine only marginally affects acute/phasic pain, and attempts to produce pre-emptive analgesia with ketamine were ineffective. This is clearly a controversial area warranting further study.

Extradural administration

The efficacy of extradural ketamine is also controversial. Naguib and colleagues[26] reported that extradural ketamine 30 mg produced potent postoperative pain relief without respiratory depression or psychic disturbance, while Schneider and Diltoer[27] showed that extradural ketamine (30 mg with 30 mg h^{-1}) provided inadequate analgesia with an associated "unpleasant feeling". Although ketamine has been reported to interact with opioid receptors[9 10], the affinity for opioid receptors may be 10 000 fold weaker than that of morphine[9]. Pharmacokinetic studies of extradural ketamine[28] and morphine[29] in dogs showed that 30 min after extradural injection the concentration ratio of cerebrospinal fluid/plasma was approximately 0.5 and 40, respectively. Therefore, it seems unlikely that extradural ketamine produces analgesia via opioid receptor occupation in the spinal cord and an effective (at the opioid receptor) extradural dose of ketamine is likely to produce not only spinal but also systemic effects, which might include general anaesthesia.

Intrathecal administration

Ketamine has been administered intrathecally (5–50 mg in 3 ml, approximately 0.2–2% solution) with or without adrenaline 0.1 mg for war casualties with lower limb injuries[4]. Ketamine 50 mg with adrenaline (but not ketamine alone) produced sensory and motor block without respiratory depression or hypotension lasting 45–90 min. Unlike the study of Dowdy, Kaya and Gocho[3] in dogs, central effects such as dizziness and drowsiness were reported in humans[4]. In animal studies[11 30 31], most investigators found that in the absence of adrenaline, ketamine-induced motor block was variable and shortlived[11 31], presumably related to increased systemic absorption. Therefore, intrathecal ketamine should be used in conjunction with adrenaline.

In summary, use of i.v., i.m., extradural or intrathecal ketamine for postoperative pain relief is clearly of limited value.

NEUROPROTECTIVE ACTION

As activation of NMDA receptors is implicated in cerebral ischaemic damage, NMDA receptor antagonists, including ketamine, have neuroprotective potential. In a study using MK-801 (an NMDA antagonist) and ketamine, Church, Zerman and Lodge reported neuroprotection after transient cerebral ischaemia in rats[32]. However, they also observed that high doses of ketamine and MK-801 produced behavioural disturbances. Hoffman and colleagues[33] showed that ketamine improved neuronal outcome from incomplete cerebral ischaemia in rats by a mechanism related to a decrease in plasma catecholamine concentrations. In contrast, Jensen and Auer[34] failed to demonstrate any protection against ischaemic damage in rats using ketamine. It is difficult to explain the discrepancy in these two studies[32 34] (both in rats), especially as the mechanisms for producing ischaemia, ischaemic time and the ketamine administration regimen were very similar. Further mechanistic studies are required to determine any neuroprotective efficacy.

CRITICAL ILL PATIENTS

Septic shock

Ketamine has been shown to reduce the need for inotropic support in septic patients[35], an effect that may be related to inhibition of catecholamine uptake[36]. In addition, infusion of ketamine resulted in better sedation, increased arterial pressure and diminution of bronchospasm in a patient with acute lymphatic leukaemia who developed bilateral fulminating pneumonia with marked agitation, hypotension and bronchospasm[37]. In this patient infusion of midazolam failed to provide adequate sedation. Several animal studies also indicated that ketamine anaesthesia may reduce pulmonary injury via a reduction in endotoxin-induced pulmonary hypertension and extravasation[38] and produce haemodynamic stability (presumably via reduction in catecholamine reuptake[36]) in a model of endotoxic shock[39]. In a recent study, Schmidt and colleagues showed that ketamine reduced endotoxin-mediated leucocyte adhesion to vessel walls[40].

Haemorrhagic shock

The sympathomimetic effects of ketamine[1] may be advantageous in patients with haemorrhagic shock compared with other conventional anaesthetics. Several clinical reports indicated that induction of anaesthesia with ketamine produced either no change or a slight increase in arterial pressure and heart rate[2]. However, ketamine should be used cautiously for shock patients as severe hypotension may occur on induction of anaesthesia. Ketamine-induced hypotension in shock may result from loss of sympathoadrenal activity that accompanies loss of consciousness[35].

Asthma

Ketamine has been used successfully in the treatment of status asthmaticus[41]. Laboratory studies indicated that the spasmolytic[42 43] and anti-inflammatory actions[38 40 44] of ketamine may contribute to its efficacy in asthma. The mechanism by which ketamine produces airway relaxation is still unclear although several mechanisms[15 42 43] have been suggested, including increased catecholamine concentrations, inhibition of catecholamine uptake, voltage-sensitive Ca^{2+} channel block and inhibition of postsynaptic nicotinic or muscarinic receptors.

In this editorial we have described the pharmacology of ketamine and discussed its clinical use. However, our knowledge of the mechanism(s) of action of ketamine is still far from complete and we hope further research with this interesting compound may provide clues to the mechanism(s) of ketamine anaesthesia and analgesia.

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References

1. Domino EF, Chidiff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic in human. *Clinical Pharmacology and Therapeutics* 1965; **6**: 279–291.
2. White PF, Way WL, Tevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56**: 119–136.
3. Dowdy EG, Kaya K, Gocho Y. Some pharmacologic similarities of ketamine, lidocaine, and procaine. *Anesthesia and Analgesia* 1973; **52**: 839–842.
4. Bion JF. Intrathecal ketamine for war surgery. A preliminary study under field conditions. *Anaesthesia* 1984; **39**: 1023–1028.
5. Durrani Z, Winnie AP, Zsigmond EK, Burnett M. Ketamine for intravenous regional anesthesia. *Anesthesia and Analgesia* 1989; **68**: 328–332.
6. Salt TE, Wilson DG, Prasad SK. Antagonism of *N*-methylasparate and synaptic responses of neurones in the rat ventrobasal thalamus by ketamine and MK-801. *British Journal of Pharmacology* 1988; **94**: 443–448.
7. Hall R, Murdoch J. Brain protection: physiological considerations. Part II: the pharmacology of brain protection. *Canadian Journal of Anaesthesia* 1990; **37**: 762–777.
8. Brockmeyer DM, Kendig JJ. Selective effects of ketamine on amino acid-mediated pathways in neuronal rat spinal cord. *British Journal of Anaesthesia* 1995; **74**: 79–84.
9. Smith DJ, Bouchal RL, DeSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, Crisp T. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* 1987; **26**: 1253–1260.
10. Hurstveit O, Maurset A, Øye I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, and muscarinic receptors. *Pharmacology and Toxicology* 1995; **77**: 355–359.
11. Crisp T, Perrotti JM, Smith DL, Stafinsky JL, Smith DJ. The local monoaminergic dependency of spinal ketamine. *European Journal of Pharmacology* 1991; **194**: 167–172.
12. Mimura MA, Namiki R, Kishi T, Ikeda T, Miyake H. Central cholinergic action produces antagonism to ketamine anaesthesia. *Acta Anaesthesiologica Scandinavia* 1992; **36**: 460–462.
13. Durieux ME. Inhibition by ketamine of muscarinic acetylcholine receptor function. *Anesthesia and Analgesia* 1995; **81**: 57–62.
14. Baum VC, Tecson ME. Ketamine inhibits transsarcolemmal calcium entry in guinea pig myocardium: direct evidence by single cell voltage clamp. *Anesthesia and Analgesia* 1991; **73**: 804–807.
15. Yamakage M, Hirshman CA, Croxton TL. Inhibitory effects of thiopental, ketamine, and propofol on voltage-dependent Ca^{2+} channels in porcine tracheal smooth muscle cells. *Anesthesiology* 1996; **83**: 1274–1282.
16. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; **367**: 607–614.
17. Mody I, MacDonald JF. NMDA receptor-dependent excitotoxicity: the role of intracellular Ca^{2+} release. *Trends in Pharmacological Science* 1995; **16**: 356–359.
18. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bjerring P, Zbinden AM. The effect of *N*-methyl-D-asparate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesthesia and Analgesia* 1995; **81**: 63–68.
19. Yamamura T, Harada K, Okamura A, Kemmotsu O. Is the site of action of ketamine anesthesia the *N*-methyl-D-asparate receptor? *Anesthesiology* 1990; **72**: 704–710.
20. Smith DJ, Perrotti JM, Mansell AL, Monroe PJ. Ketamine analgesia is not related to an opiate action in the periaqueductal gray region of the rat brain. *Pain* 1985; **21**: 253–265.
21. Benoit E, Carratù MR, Dubois JM, Mitolo-Chieppa D. Mechanism of action of ketamine in the current and voltage clamped myelinated nerve fibre of the frog. *British Journal of Pharmacology* 1986; **87**: 291–297.
22. Frenkel C, Urban BW. Molecular actions of racemic ketamine on human CNS sodium channels. *British Journal of Anaesthesia* 1992; **69**: 292–297.
23. Sikand KS, Smith G, Lambert DG. Ketamine inhibits K^+ evoked [^{3}H]noradrenaline release from SH-SY5Y cells by reducing calcium influx. *Biochemical Society Transactions* 1995; **23**: 417S.
24. Dich-Nielsen JO, Svendsen LB, Berthelsen P. Intramuscular low-dose ketamine versus pethidine for postoperative pain treatment after thoracic surgery. *Acta Anaesthesiologica Scandinavia* 1992; **36**: 583–587.
25. Owen H, Reekie RM, Clements JA, Watson R, Nimo WS. Analgesia from morphine and ketamine. *Anaesthesia* 1987; **42**: 1051–1056.
26. Naguib M, Adu-Gyamfi Y, Absood GH, Farag H, Gyasi HK. Extradural ketamine for postoperative analgesia. *Canadian Anaesthetists Society Journal* 1986; **33**: 16–21.
27. Schneider I, Diltoer M. Continuous extradural infusion of

ketamine during labour. *Canadian Journal of Anaesthesia* 1987; 34: 657–658.

28. Pedraz JL, Calvo MB, Gason AR, Hernandez R, Muriel C, Torres LM, DominguezGil A. Pharmacokinetics and distribution of ketamine after extradural administration to dogs. *British Journal of Anaesthesia* 1991; **67**: 310–316.
29. Durant PAC, Yaksh TL. Distribution in cerebrospinal fluid, blood, and lymph of extradurally injected morphine and inulin in dogs. *Anesthesia and Analgesia* 1986; **65**: 583–592.
30. Ahuja BR. Analgesic effect of intrathecal ketamine in rats. *British Journal of Anaesthesia* 1983; 55: 991–995.
31. Borgbjerg FM, Sevensson BA, Frigast C, Gordh T. Histopathology after repeated intrathecal injections of preservative-free ketamine in rabbit: a light and electron microscopic examination. *Anesthesia and Analgesia* 1994; **79**: 98–104.
32. Church J, Zerman S, Lodge D. The neuroprotective action of ketamine and MK-801 after transient cerebral ischemia in rats. *Anesthesiology* 1988; **69**: 702–709.
33. Hoffman WE, Pelligrino D, Werner C, Kochs E, Albrecht RF, Schulte am Esch J. Ketamine decreases plasma catecholamines and improves outcome from incomplete cerebral ischemia in rats. *Anesthesiology* 1992; **76**: 755–762.
34. Jensen ML, Auer RN. Ketamine fails to protect against ischaemic neuronal necrosis in the rat. *British Journal of Anaesthesia* 1988; **61**: 206–210.
35. Yli-Hankala A, Kirvel M, Randell T, Lindgren L. Ketamine anaesthesia in a patient with septic shock. *Acta Anaesthesiologica Scandinavia* 1992; **36**: 483–485.
36. Lundy PM, Lockwood PA, Thompson G, Frew R. Differential effects of ketamine isomers on neuronal and extraneuronal catecholamine uptake mechanisms. *Anesthesiology* 1986; **64**: 359–363.
37. Park GR, Manara AR, Mendel L, Bateman PE. Ketamine infusion. Its use as a sedative, inotrope and bronchodilator in a critically ill patient. *Anaesthesia* 1987; **42**: 980–983.
38. Bodai BI, Harms BA, Nottingham PB, Zaiss C, Demling RH. The effect of ketamine on endotoxin-induced lung injury. *Anesthesia and Analgesia* 1983; **62**: 398–403.
39. Van der Linden P, Girbart E, Engelman E, Schmartz D, de Rood M, Vincent JL. Comparison of halothane, isoflurane, alfentanil, and ketamine in experimental septic shock. *Anesthesia and Analgesia* 1990; **70**: 608–617.
40. Schmidt H, Ebeling D, Bauer H, Bach A, Bohrer H, Gebhard MM, Martin E. Ketamine attenuates endotoxin-induced leukocyte adherence in rat mesenteric venules. *Critical Care Medicine* 1995; **23**: 2008–2014.
41. Sarma VJ. Use of ketamine in acute severe asthma. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 106–107.
42. Wilson LE, Hatch DJ, Rehder K. Mechanisms of the relaxant action of ketamine on isolated porcine trachealis muscle. *British Journal of Anaesthesia* 1993; 71: 544–550.
43. Hirota K, Sato T, Rabito SF, Zsigmond EK, Matsuki A. Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle. *British Journal of Anaesthesia* 1996; **76**: 266–270.
44. Hirota K, Zsigmond EK, Matsuki A, Rabito SF. Topical ketamine inhibits albumin extravasation in chemical peritonitis in rats. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 174–178.

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CLINICAL INVESTIGATIONS

Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination

J.E. MONTGOMERY, C.J. SUTHERLAND, I.G. KESTIN AND J.R. SNEYD

Summary

Paracetamol and diclofenac have different mechanisms of action, and the combination may be more effective than each drug used alone in treating postoperative pain. In a double-blind, controlled design, we studied 60 patients undergoing elective abdominal gynaecological surgery, who received suppositories of paracetamol 1.5 g, diclofenac 100 mg or a combination of the two before the start of surgery. Patients received morphine in the intraoperative period, and cumulative morphine use from a patient-controlled analgesia system was recorded to measure the analgesic effect of the suppositories. Morphine consumption was greatest in the group that received paracetamol alone and lowest in the group given the combination ($P<0.01$). There was no difference in the incidence of morphine-related side effects between the groups. We conclude that a diclofenac–paracetamol combination reduced the amount of morphine used compared with paracetamol alone. (*Br. J. Anaesth.* 1996;**77**:445–447)

Key words

Analgesics opioid, morphine. Analgesics non-opioid, diclofenac. Analgesics non-opioid, paracetamol. Pain, postoperative.

Non-steroidal anti-inflammatory drugs (NSAID), such as diclofenac, are effective in the treatment of postoperative pain. If given with opioids, the amount of opioid required is reduced with a consequent reduction in side effects[1–3]. In clinical studies, some patients with osteoarthritic pain found paracetamol to be as efficacious as NSAID, and it does not have the side effects of gastric irritation, altered platelet function or exacerbation of asthma[4 5]. Diclofenac and paracetamol have different mechanisms of action and the combination may be more effective than either drug used alone. We have undertaken a prospective, randomized, double-blind, comparative study to assess the analgesic efficacy of paracetamol alone and in combination with diclofenac.

Patients and methods

With Ethics Committee approval and written informed patient consent, we studied 60 women, ASA I or II, aged 25–65 yr, undergoing elective abdominal gynaecological surgery. We excluded women weighing more than 100 kg, those unable to use a patient-controlled analgesia system (PCA) for postoperative pain control and those with a history of peptic ulceration, bleeding disorders, impaired renal or hepatic function, or sensitivity to NSAID or paracetamol. Patients received temazepam 20–30 mg, 1 h before operation and anaesthesia was induced with thiopentone 3–5 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was given to facilitate orotracheal intubation. Morphine 0.1–0.15 mg kg^{-1} was given as an i.v. bolus before the start of surgery; additional boluses were given during surgery if required up to a total of 0.2 mg kg^{-1}. Anaesthesia was maintained with 0.5–2% enflurane and 60% nitrous oxide in oxygen.

Patients were allocated randomly to one of three groups by opening a sealed envelope, after induction of anaesthesia. Allocation was decided using random numbers generated by Claris Works software. Group P received a rectal suppository of paracetamol 1.5 g; group D received a rectal suppository of diclofenac 100 mg; and group PD received rectal suppositories of paracetamol 1.5 g and diclofenac 100 mg. The suppositories were given before the start of surgery.

At the end of surgery, residual neuromuscular block was antagonized with glycopyrronium 0.5 mg and neostigmine 2.5 mg. In the recovery area patients received morphine 2 mg i.v. at 5-min intervals until they described their pain as mild or absent. A PCA system (Graseby 3300, Graseby Medical Ltd, Watford, Herts) programmed to give a bolus of morphine 1 mg with droperidol 50 µg, with a 5-min lockout time and no background infusion, was connected to a dedicated i.v. cannula. Prochlorperazine 12.5 mg i.m. every 6 h if required and oxygen for the first 6 h were prescribed.

The amount of morphine given before connection to the PCA system and duration of anaesthesia and recovery were recorded. Hourly cumulative morphine requirements were recorded from the electronic memory of the PCA system. At 6 and 24 h after operation, patients were visited by an investigator who was unaware of the treatment group, and asked to complete two 10-cm visual analogue scales (VAS), one for pain and one for nausea. Both scales ranged from none to worst possible. The VAS for pain was recorded on deep breathing, as this has been shown to be more reproducible than a pain

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score obtained at rest[6]. At these times the investigator also recorded a sedation score: 0=fully awake; 1=drowsy; 2=sleeping but responds to gentle stimulus; 3=sleeping no response to gentle stimulus. The nurses recorded routinely pain and sedation scores and ventilatory frequency every hour for 6 h, and every 2 h thereafter.

The sample size was chosen by *a priori* power calculation to provide 80% probability of demonstrating a reduction in the use of morphine by 30% when $\alpha=0.05$. Results were analysed using repeated measures one-way analysis of variance for morphine consumption, one-way analysis of variance and Fisher's exact test; paired comparisons were made using Student's t test with Bonferroni correction for parametric data and Dunn's test for non-parametric data. The level of significance was 5%.

Results

One woman, who received both paracetamol and diclofenac, was excluded from the analysis as she was unable to use the PCA because of severe vomiting and requested alternative analgesia 19 h after operation. Of the remaining 59 women, 20 received paracetamol, 20 received diclofenac and 19 received both.

There were small but statistically significant differences in age and body mass index between the three groups. Women who received both paracetamol and diclofenac were significantly older than those who received paracetamol (mean age 44.5 yr compared with 38.1 yr, $P=0.02$) (table 1). Body mass index for those given paracetamol was significantly less than for either of the other groups (22 compared with 26.1 and 24.4, $P<0.02$) (table 1). Duration of anaesthesia and amount of time spent in recovery were similar in all three groups (table 1).

The amount of morphine required before the start of the PCA was similar in each group (mean 12.5 mg, 14.8 mg and 13.4 mg) (table 2). Patients receiving paracetamol used significantly more morphine over the 24 h than those given paracetamol and diclofenac ($P<0.05$) (fig. 1, table 2). Women given diclofenac used an intermediate amount of morphine, although this was not significantly different from the two other groups (fig. 1). VAS pain scores were similar between groups (table 2).

There were no differences between the groups in any of the measures of nausea and vomiting (table 3), and sedation scores were similar between groups. No patient had a ventilatory frequency of less than 10 bpm. One patient, who received both paracetamol and diclofenac, required transfusion because of excessive blood loss during difficult surgery. No other patient required blood transfusion.

Table 1 Patient characteristics and recovery times (mean (SD or range)). $^{*}P < 0.05$ compared with combination group; $^{\dagger}P < 0.05$ compared with the two other groups

	Paracetamol (n=20)	Diclofenac (n=20)	Combination (n=19)
Age (yr)	38.1 (24–53)*	40.5 (26–60)	44.5 (33–59)
Body mass index	22 (17.5–30.8)†	26.1 (17.2–34.4)	24.4 (18.7–31.8)
Duration of anaesthesia (min)	94.4 (26.9)	94.7 (18.9)	97.3 (23.3)
Time in recovery (min)	71.1 (20.3)	72.5 (36.4)	68.9 (25.5)

Table 2 Pain scores and morphine use (mean (95% confidence intervals (CI))). $^{**}P < 0.01$ compared with paracetamol group (ANOVA)

	Paracetamol (n=20)	Diclofenac (n=20)	Combination (n=19)
Morphine during anaesthesia	11.1 (9.9–12.2)	11.7 (10.1–13.3)	11.9 (10.4–13.3)
Morphine in recovery area	1.5 (0.3–2.7)	3.1 (1.5–4.6)	1.5 (0–3.1)
Morphine from PCA, 0–6 h	16.4 (11.7–20.1)	14.1 (10.7–17.3)	9.4 (6.7–12.1)**
Morphine from PCA, 0–24 h	44.9 (36.1–53.6)	34.5 (27.4–41.6)	27.1 (18.5–35.8)**
Pain VAS, 6 h (median (range))	3.3 (0.0–7.1)	1.7 (0.3–5.1)	2.6 (0.0–7.9)
Pain VAS, 24 h (median (range))	3.4 (0.2–9.2)	1.9 (0.0–7.2)	2.1 (0.2–4.6)

Table 3 Sedation and nausea and vomiting scores (median (range))

	Paracetamol (n=20)	Diclofenac (n=20)	Combination (n=19)
Sedation score at 6 h	2 (0–2)	2 (0–2)	2 (2–0)
Sedation score at 24 h	0 (0–2)	0 (0–2)	0 (0–2)
Nausea VAS at 6 h	0.65 (0–6.7)	0.3 (0–4.4)	0.6 (0–5)
Nausea VAS at 24 h	2.6 (0–8.8)	2.3 (0—.6)	1 (0–5.5)
Incidence of vomiting	8 (40%)	6 (30%)	5 (26%)

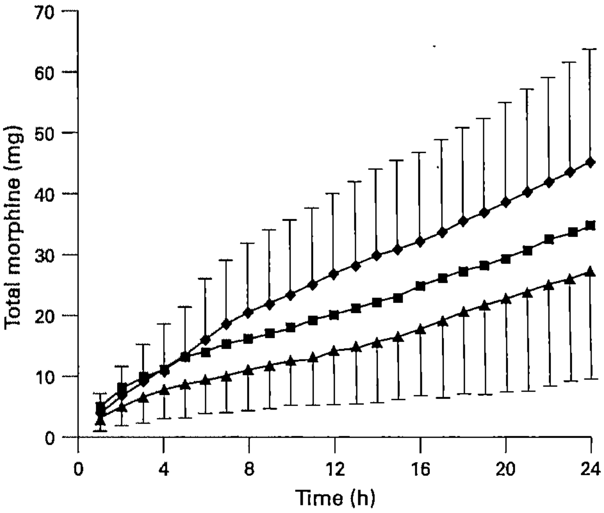

Figure 1 Cumulative morphine consumption (mean, SD) in the paracetamol (♦), diclofenac (■) and combination (▲) groups . For clarity error bars are omitted from the diclofenac group. At 6, 12, 18 and 24 h, the SD values of this group were 7.0, 9.0, 12.4 and 15.1 mg, respectively

Discussion

The use of a combination of paracetamol with other NSAID has been shown to improve analgesia in dental and other pain models[7–9]. In our study, patients used a PCA system and therefore the effects of the drugs were measured by morphine consumption, not by differences in analgesia. Diclofenac and paracetamol have different mechanisms of action and their actions may therefore be additive or synergistic. The use of the combination reduced the amount of morphine required during the first 24 h after operation compared with paracetamol alone. Patients who received both drugs used less morphine than those who received diclofenac alone, but this was not statistically significant. We would need to study approximately 100 patients per group for these differences to be statistically significant.

We did not include a placebo control group, who would have received morphine PCA alone, as a previous study has shown that diclofenac reduces morphine requirements, with reduced pain scores at 4 h after surgery[3].

The dose of paracetamol used (1.5 g) was higher than the normal oral paracetamol dose, as the bioavailability of suppositories is lower than tablets[10] and only a single dose was given. Recent studies in children receiving rectal paracetamol have shown that doses as high as 35 mg kg^{-1} may be needed to achieve plasma concentrations in the therapeutic range[11]. It may be that the initial dose of rectal paracetamol needs to be larger than currently recommended to provide better analgesia; further studies are needed to assess this.

Patients in the paracetamol group had a significantly lower body mass index than the two other groups, however, the effective dose of morphine is not necessarily dose related[12]. Women in the paracetamol group were also slightly younger than in the combination group, which would be likely to increase morphine consumption. However, morphine consumption is very variable between patients and the age difference was small, therefore we believe that this was unlikely to have had an important effect. The incidence and severity of nausea and vomiting were similar to those reported in other studies where droperidol was used in the PCA and were similar between groups[13]; if droperidol had not been included it may have been possible to show between-group differences.

In conclusion, the use of a diclofenac–paracetamol combination reduced the amount of morphine required for adequate analgesia by about one-third compared with paracetamol alone.

References

1. Moffat AC, Kenny GNC, Prentice JW. Postoperative nefopam and diclofenac. Evaluation of their morphine-sparing effect after upper abdominal surgery. *Anaesthesia* 1990; **45**: 302–305.
2. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effect of ketorolac tromethamine. A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. *Anaesthesia* 1987; **42**: 727–731.
3. Hodsman NBA, Burns J, Blyth A, Kenny GNC, McArdle CS, Rotman H. The morphine sparing effects of diclofenac sodium following abdominal surgery. *Anaesthesia* 1987; **42**: 1005–1008.
4. March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. n of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthitis. *British Medical Journal* 1994; **309**: 1041–1046.
5. Elliott SL. The comparative saftey of paracetamol and non-steroidal anti-inflammatory drugs. *Australian Prescriber* 1993; **16**: 93–95.
6. Gould TH, Crosby DL, Harmer M, Lloyd SM, Lunn JN, Rees GAD, Roberts DE, Webster JA. Policy for controlling pain after surgery: effect of sequential changes in management. *British Medical Journal* 1992; **305**: 1187–1193.
7. Davie IT, Gordon NH. Comparative assessment of fenoprofen and paracetamol given in combination for pain after surgery. *British Journal of Anaesthesia* 1978; **50**: 931–935.
8. Olstad OA, Skjelbred P. The effects of indoprofen vs paracetamol on swelling, pain and other events after surgery. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1986; **24**: 34–38.
9. Schachtel BP, Thoden WR, Baybutt RI. Ibuprofen and acetaminophen in the relief of postpartum episiotomy pain. *Journal of Clinical Pharmacology* 1989; **29**: 550–553.
10. Seideman P, Alvan G, Andrews RS, Labross A. Relative bioavailability of a paracetamol suppository. *European Journal of Clinical Pharmacology* 1980; **17**: 465–468.
11. Houck CS, Sullivan LJ, Wilder RT, Rusy LM, Burrows FA. Pharmacokinetics of a higher dose of rectal acetaminophen in children. *Anesthesiology* 1995; **83**: A1126.
12. Burns JW, Hodsman NBA, McLintock TCC, Gillies GWA, Kenny GNC, McArdle CS. The influence of patient characteristics on the requirements for postoperative analgesia. *Anaesthesia* 1989; **44**: 2–6.
13. Barrow PM, Hughes DG, Redfern N, Urie J. Influence of droperidol on nausea and vomiting during patient-controlled analgesia. *British Journal of Anaesthesia* 1994; **72**: 460–461.

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Postoperative pulmonary function after laparoscopic and open cholecystectomy

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Summary

In this prospective, randomized study, we compared 42 patients undergoing laparoscopic cholecystectomy and 40 undergoing open cholecystectomy to determine if laparoscopic cholecystectomy results in less respiratory impairment and fewer respiratory complications. Pulmonary function tests, arterial blood-gas analysis and chest radiographs were obtained in both groups before operation and on the second day after operation. Postoperative pain scores and analgesic requirements were also recorded. After operation, a significant reduction in total lung capacity, functional residual capacity (FRC), forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and mid-expiratory flow ($FEF_{25-75\%}$) occurred after both laparoscopic and open cholecystectomy. The reductions in FRC, FEV_1, FVC and $FEF_{25-75\%}$ were smaller after laparoscopic (7%, 22%, 19% and 23%, respectively) than after open (21%, 38%, 32% and 34%, respectively) cholecystectomy. Laparoscopic cholecystectomy was also associated with a significantly lower incidence (28.6% *vs* 62.5%) and less severe atelectasis, better oxygenation and reduced postoperative pain and analgesia use compared with open cholecystectomy. We conclude that postoperative pulmonary function was impaired less after laparoscopic than after open cholecystectomy. (*Br. J. Anaesth.* 1996;**77**:448–452)

Key words

Lung, atelectasis. Complications, respiratory. Surgery, laparoscopy. Surgery, gastrointestinal. Lung, function.

Cholecystectomy performed via laparotomy is associated with postoperative pulmonary dysfunction which increases the risk of postoperative pulmonary complications. The site and size of the surgical incision, severity of postoperative pain and impaired diaphragmatic function are the most important factors known to impair pulmonary function after conventional open cholecystectomy[1–5].

Laparoscopic cholecystectomy is a new technique that has become the treatment of choice for symptomatic cholelithiasis[6]. The procedure is associated with the absence of skin incision, less pain, shorter hospitalization and faster recovery compared with open cholecystectomy[6–8]. Minimal pulmonary dysfunction after laparoscopic cholecystectomy in healthy patients has been reported by several authors[9–14]. However, in most studies only expiratory lung volumes were evaluated and postoperative respiratory complications were not studied. In addition, these were observational or non-randomized studies, limited to a small number of patients, and could have exaggerated the advantages of laparoscopic cholecystectomy.

We have therefore compared changes in respiratory function after laparoscopic and conventional open cholecystectomy in a prospective, randomized study.

Patients and methods

All patients with symptomatic cholelithiasis, undergoing elective cholecystectomy under general anaesthesia, were considered for entry into this study. Exclusion criteria were acute cholecystitis, choledocholithiasis, age more than 65 yr and obesity (body mass index >29 kg m^{-2}). Patients with a history of previous pulmonary disease, those smoking more than 10 cigarettes per day and patients not accepting randomization were also excluded. The study was planned according to the Helsinki declaration and was approved by our hospital's Research Ethics Committee. After giving informed consent, suitable patients were allocated randomly, by selecting closed envelopes, to a surgical team capable of performing each procedure.

Anaesthetic and operative procedures were standardized for each group. Diazepam 10 mg was given orally for premedication 60 min before surgery. General anaesthesia was induced with fentanyl 2 μg kg^{-1} and thiopentone 5 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was given to facilitate intubation of the trachea. Anaesthesia was maintained with 1% isoflurane and 60% nitrous oxide in oxygen, fentanyl and pancuronium. The lungs of all patients were ventilated mechanically with a tidal volume of 8–10 ml kg^{-1} and ventilatory frequency was adjusted to maintain an end-tidal carbon dioxide partial pressure of 4.0–4.3 kPa. During operation, patients were monitored continuously for heart rate, arterial pressure, oxygen

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saturation (as measured by pulse oximetry) and partial pressure of carbon dioxide in exhaled gas (end-tidal carbon dioxide). Arterial blood samples for gas analysis were obtained just before insufflation, during dissection of the cystic pedicle and before desufflation.

All operations were performed in the morning after an overnight fast. All patients had a nasogastric tube and urinary catheter inserted, and these were removed immediately after surgery. Open cholecystectomies were performed through a transverse right subcostal incision, 10–12 cm long, with partial transection of the ipsilateral rectus abdominis muscle. Laparoscopic cholecystectomies were performed via a four trocar technique, as described previously[15], pneumoperitoneum was established with carbon dioxide insufflation and the intra-abdominal pressure was maintained at 14 mm Hg.

PULMONARY FUNCTION STUDIES

Static and dynamic lung volumes and flow rates were measured using Jaeger's Bodybox and pneumotachograph (Bodyscreen II, Jaeger, Germany). Measurements were made with the patient in the sitting position, according to the guidelines of the American Thoracic Society[16]. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), mid-expiratory flow ($FEF_{25-75\%}$), functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC) and airway resistance (*R*aw) were measured and the greatest value of three attempts was recorded, except for FRC which was defined as the mean of three measurements. RV/TLC and FEV_1/FVC ratios were also calculated. Arterial blood-gas analysis was performed just before the spirometric studies using an automatic analyser (ABL-3, Radiometer, Copenhagen, Denmark). All tests were performed in our respiratory laboratory by the same physician who was unaware of the nature of the study.

Posteroanterior and lateral chest radiographs were obtained at maximal inspiration with the patient in the upright position. Chest radiographs were interpreted by a qualified radiologist who was unaware of the type of procedure and whether the x-ray was performed before or after operation. Atelectasis was graded as micro-, focal, segmental or lobar. Pneumonia was defined as the simultaneous presence of radiological and physical signs, and positive culture results.

All studies were performed on the day before surgery and in the morning of the second postoperative day. Postoperative spirometry was performed if the VAS pain score, estimated at rest just before testing, was less than 4 cm.

PAIN ASSESSMENT

Intensity of postoperative pain was estimated using a linear 0–10 cm (0=no pain, 10=severe pain) visual analogue scale (VAS). Assessments were made when the patient arrived at the recovery ward, 4 and 12 h after the end of surgery, and thereafter at 08:00, 14:00 and 20:00 every day after operation. To standardize postoperative analgesia, pethidine 0.5 mg kg^{-1} i.m. was administered to all patients, as requested by the patient. Pain charts were collected every day by an independent observer and the daily recorded numerical pain scores were summed for each patient. Analgesic use was also calculated on a daily basis as the total quantity of pethidine administered.

STATISTICAL ANALYSIS

All data are presented as mean (SD) values except for pain scores and pethidine consumption where the median (interquartile range) value is used. Statistical analysis was performed using the Statgraphics 5.1 statistical software package (Statistical Graphics Corporation, Rockville, MD, USA). Quantitative data were analysed by paired and unpaired *t* test and categorical data by chi-square test. Differences in pulmonary function variables within each group were evaluated by the paired *t* test. Perioperative changes were calculated and statistical comparisons between groups were made using the unpaired *t* test. The overall incidence and severity of atelectasis between groups were compared by the chi-square test for trend. The Mann–Whitney *U* test was used to compare pain scores and analgesic requirements. Significance was presumed at $P<0.05$.

Results

During the study period (March 1992 to November 1993), 147 patients fulfilling the selection criteria were admitted for elective cholecystectomy. Informed consent to randomization was obtained from 98 patients. Seven patients (two allocated for laparoscopic and five for open cholecystectomy) declined to take part after randomization. Two patients from the laparoscopic cholecystectomy group were excluded because of incomplete recording of pulmonary function tests. Three patients randomized for laparoscopic cholecystectomy required conversion to open cholecystectomy as a result of difficulties in defining anatomy. These patients were also excluded. Four patients scheduled for open cholecystectomy were excluded from the study because they underwent common bile duct exploration. Thus 82 patients completed the study: 42 patients underwent laparoscopic and 40 open cholecystectomy. The two study groups were similar in patient characteristics, and anaesthetic and operative times. Duration of postoperative hospital stay was significantly shorter after laparoscopic cholecystectomy (table 1).

Preoperative pulmonary function tests and arterial blood-gas values were normal and did not differ significantly between the two groups. After operation, a significant reduction ($P<0.05$) in TLC, FRC, FEV_1,

Table 1 Clinical details of patients undergoing laparoscopic (LC) or open (OC) cholecystectomy (mean (SD or range)). *$P<0.05$ between groups (*t* test)

Variable	LC (n=42)	OC (n=40)
Age (yr)	57.1 (32–79)	56.1 (34–76)
Sex (M/F)	18/24	18/22
Weight (kg)	76.2 (12.8)	78.2 (15.1)
Height (cm)	161 (9.1)	163 (8.3)
Operative time (min)	108 (23)	97 (19)
Anaesthesia time (min)	139 (18)	116 (15)
Postoperative hospital stay (days)	2.04 (0.62)	5.65 (1.16)*

Table 2 Postoperative changes (mean (SD)) in pulmonary function variables and arterial blood-gas values after laparoscopic cholecystectomy. *$P < 0.05$ compared with preoperative values (paired t test)

Variable	Preoperative	Postoperative	Perioperative change
*R*aw (kPa litre^{-1} s^{-1})	0.27 (0.08)	0.30 (0.12)	0.025 (0.11)
TLC (litre)	4.98 (1.11)	4.34 (0.94)*	−0.63 (0.57)
RV (litre)	1.78 (0.50)	1.73 (0.52)	−0.05 (0.39)
RV/TLC (%)	36.54 (9.15)	40.77 (11.5)*	4.23 (8.41)
FRC (litre)	2.55 (0.66)	2.34 (0.60)*	−0.20 (0.40)
FEV$_1$ (litre)	2.80 (1.01)	2.16 (0.79)*	−0.64 (0.65)
FVC (litre)	3.22 (1.06)	2.55 (0.85)*	−0.66 (0.52)
FEV$_1$/FVC (%)	82.71 (11.49)	85.52 (17.51)	2.80 (12.82)
FEF$_{25-75\%}$ (litre)	3.18 (1.17)	2.44 (1.09)*	−0.74 (0.65)
pH	7.38 (0.04)	7.37 (0.04)	−0.007 (0.04)
Pa_{CO_2} (kPa)	4.92 (0.39)	5.03 (0.30)	0.11 (0.42)
Pa_{O_2} (kPa)	11.31 (0.79)	11.15 (0.65)	−0.16 (0.51)

Table 3 Postoperative changes (mean (SD)) in pulmonary function variables and arterial blood-gas values after open cholecystectomy. *$P < 0.05$ compared with preoperative values (paired t test); †$P < 0.05$ between groups (t test)

Variable	Preoperative	Postoperative	Perioperative change
*R*aw (kPa litre^{-1} s^{-1})	0.26 (0.10)	0.31 (0.15)	0.048 (0.17)
TLC (litre)	5.12 (1.21)	4.33 (1.03)*	−0.79 (0.66)
RV (litre)	1.88 (0.66)	1.81 (0.68)	−0.07 (0.43)
RV/TLC (%)	37.13 (9.51)	42.61 (12.37)*	5.47 (10.00)
FRC (litre)	2.68 (0.63)	2.08 (0.51)*	−0.60 (0.40)†
FEV$_1$ (litre)	2.89 (0.74)	1.76 (0.53)*	−1.12 (0.62)†
FVC (litre)	3.27 (0.90)	2.2 (0.69)*	−1.07 (0.56)†
FEV$_1$/FVC (%)	80.42 (8.96)	82.77 (21.17)	2.35 (19.42)
FEF$_{25-75\%}$ (litre)	2.95 (1.02)	1.95 (0.80)*	−1.00 (0.54)†
pH	7.38 (0.05)	7.38 (0.04)	−0.004 (0.05)
Pa_{CO_2} (kPa)	4.89 (0.38)	5.01 (0.35)	0.11 (0.38)
Pa_{O_2} (kPa)	11.33 (0.77)	10.65 (0.83)*	−0.68 (0.50)†

FVC and FEF$_{25-75\%}$ occurred after laparoscopic (table 2) and open cholecystectomy (table 3). However, mean reductions in FRC, FEV$_1$, FVC and FEF$_{25-75\%}$ after laparoscopic cholecystectomy (0.20 (0.40) litre (7 (13)%), 0.64 (0.65) litre (22 (17)%), 0.66 (0.52) litre (19 (16)%) and 0.74 (0.65) litre (23 (21)%), respectively) were significantly ($P<0.05$) smaller compared with those after open cholecystectomy (0.60 (0.40) litre (21 (12)%), 1.12 (0.62) litre (38 (17)%), 1.07 (0.56) litre (32 (19)%) and 1.00 (0.54) litre (34 (15)%), respectively). The RV/TLC ratio increased significantly in both groups ($P<0.05$). Changes in *R*aw, RV and FEV$_1$/FVC ratio were minimal and not significant in both groups. Arterial blood-gas analysis revealed better oxygenation after laparoscopic cholecystectomy (Pa_{O_2}=11.15 (0.65) *vs* 10.65 (0.83) kPa; $P<0.05$). Arterial pH and Pa_{CO_2} remained unchanged in both groups.

Table 4 Postoperative atelectasis after laparoscopic (LC) or open (OC) cholecystectomy. *$P < 0.05$ between groups (chi-square test for trend)

	LC (n=42)	OC (n=40)
Microatelectasis	7	14
Focal	3	7
Segmental	2	3
Lobar	0	1
Normal	30	15*

All preoperative chest radiographs were interpreted as normal. The overall incidence of postoperative atelectasis was significantly higher after open cholecystectomy (62.5% *vs* 28.6%; overall chi-square=10.09, df=4, $P<0.05$) (table 4). Atelectasis was also more severe after open cholecystectomy (chi-square for trend=7.05, df=1, $P<0.05$). Patients who developed atelectasis in the open cholecystectomy group had lower Pa_{CO_2} values compared with those without atelectasis (10.2 (0.9) *vs* 11.0 (0.8) kPa, $P<0.05$). In contrast, postoperative Pa_{CO_2} values in the laparoscopic cholecystectomy group were not significantly different between patients with and without atelectasis (10.9 (0.7) *vs* 11.3 (0.6) kPa). No patient was diagnosed as having pneumonia.

Postoperative pain scores and pethidine analgesia use during the study were significantly less in the laparoscopic cholecystectomy group (table 5).

Discussion

When this study was designed the authors had experience of performing 40 laparoscopic cholecystectomies. At that time many surgeons were critically examining the benefits of the procedure and there were surgeons at our institution who were not performing laparoscopic cholecystectomy. A randomized study of laparoscopic compared with open cholecystectomy was justified. As the study proceeded, ethical problems arose, as experienced by other authors[17]. In addition, the wide media publicity resulted in high motivation among patients to undergo only laparoscopic cholecystectomy. The highest rate of non-acceptance and all withdrawals after randomization were observed during the last 6 months of the study. Men were more keen to participate in the study and this was reflected in the relatively higher than expected male/female ratio in this study.

To our knowledge, there has been no other randomized study comparing pulmonary function after laparoscopic and open cholecystectomy. Results from this study indicated that considerable impairment of pulmonary function occurred after laparo-

Table 5 Daily pain scores (VAS) and analgesic requirements (median (interquartile range)) after laparoscopic (LC) or open (OC) cholecystectomy. *$P < 0.05$ between groups (Mann–Whitney U test)

	VAS (cm)		Pethidine (mg day^{-1})	
	LC (n=42)	OC (n=40)	LC (n=42)	OC (n=40)
Day of surgery	4 (4–5)	5 (4–6)*	60 (46–87)	80 (70–120)*
1st postoperative day	3 (2–4)	4 (3–5)*	30 (0–40)	135 (105–160)*
2nd postoperative day	2 (1–2)	3 (2–4)*	0 (0–34)	90 (70–120)*

scopic cholecystectomy in otherwise healthy patients. The patterns of postoperative alterations were qualitatively similar but quantitatively less than those after open cholecystectomy. In previous observational[13,14] and non-randomized controlled[9–12,18,19] studies, the postoperative reduction in FVC, FEV_1 and $FEF_{25-75\%}$ ranged from 20% to 40% on the first or second postoperative day after laparoscopic and from 40% to 70% after open cholecystectomy in healthy patients. A significant reduction in TLC after laparoscopic (8% to 17%) and after open (22%) cholecystectomy was also observed[13,19], while RV was unchanged[13,14]. FRC has been reported to decrease 24 h after laparoscopic cholecystectomy by 7% to 15% of preoperative values[13,14] compared with a reduction of 36% after open cholecystectomy[18]. The patterns and magnitude of the changes in pulmonary function after laparoscopic or open cholecystectomy observed in this study are in agreement with those mentioned above. The small discrepancies may possibly be related to differences in patient selection criteria, duration of anaesthesia and surgery, and measurements at different postoperative times. However, the most important finding is that laparoscopic cholecystectomy is associated with less impairment of pulmonary function compared with open cholecystectomy.

Upper abdominal surgery performed through a subcostal or midline incision is associated with significant alterations in pulmonary function. A restrictive breathing pattern with reduced inspiratory capacity is evident immediately after surgery[1,2]. A shift from abdominal to thoracic breathing occurs because of the reduced diaphragmatic contribution to tidal volume[4,5,20]. Although the aetiology of pulmonary dysfunction after upper abdominal surgery is not completely elucidated, postoperative pain[3,20,21] and diaphragmatic dysfunction[4,5] are considered to be the major contributing factors. Pain scores and analgesic requirements in this study were reported up to the second postoperative day as at that time most of the patients undergoing laparoscopic cholecystectomy were discharged from hospital. Decreased pain scores and reduced analgesic requirements, observed during this period of time, confirmed the clinical observations that laparoscopic cholecystectomy was accompanied by less postoperative pain. However, it is not evident if less postoperative pain is the only factor responsible for less impairment of pulmonary function after laparoscopic cholecystectomy. Extradural analgesia provides adequate pain relief but does not improve pulmonary function after laparoscopic cholecystectomy[10]. Therefore, diaphragmatic dysfunction after laparoscopic cholecystectomy should be considered also. Diaphragmatic contribution to tidal volume during quiet breathing was found to be unchanged immediately after laparoscopic cholecystectomy[22]. However, 3 h after surgery a shift from abdominal to thoracic breathing associated with a 30% reduction in total tidal volume and an increased breathing frequency were observed[23]. This rapid and shallow breathing pattern led to an increase in end-tidal carbon dioxide concentration by 9%. There was no evidence of altered contractility and changes in breathing pattern were attributed to reflex inhibition of diaphragmatic inspiratory activity. Impaired diaphragmatic function early after laparoscopic cholecystectomy with gradual restoration over 24 h was documented also by direct diaphragmatic electromyography[24]. Alterations in rib cage–abdominal partitioning with reduction in abdominal tidal volume during resting and coached abdominal breathing by 32% and 29%, respectively, and shortening of the inspiratory time were observed 24 h after laparoscopic cholecystectomy[25]. These findings suggest that diaphragmatic dysfunction, similar to that in the open procedure, does occur after laparoscopic cholecystectomy. This is not unexpected as the intra-abdominal site of intervention is the same in both procedures. Manipulation and local stimulation of the gallbladder and its bed during laparoscopic cholecystectomy may elicit reflex inhibition of the diaphragm, as has been shown in animal studies[26].

Postoperative alterations in pulmonary function are clinically important if they contribute to respiratory complications. The decrease in FRC and its relation to the closing capacity have been shown to correlate well with postoperative atelectasis and hypoxaemia[2,27,28]. The development of atelectasis after laparoscopic cholecystectomy has been evaluated in two other studies. Johnson and colleagues[14] reported that segmental atelectasis developed in three of 31 patients undergoing laparoscopic cholecystectomy. In the study of Schauer and colleagues[19], radiological atelectasis of varying degrees occurred in 40% of patients after laparoscopic cholecystectomy compared with 95% of patients after open cholecystectomy. This high rate of atelectasis was probably a result of the fact that many patients in that study had risk factors for postoperative pulmonary complications. In our study in healthy patients, the incidence and severity of postoperative atelectasis were significantly reduced and Pa_{O_2} values were higher after laparoscopic cholecystectomy. Better oxygenation after laparoscopic cholecystectomy compared with open cholecystectomy has been also reported by other authors[9,11,18]. Although these findings parallel the changes in FRC, it is difficult to ascertain if the smaller reduction in FRC after laparoscopic cholecystectomy observed in our study translates into fewer respiratory complications.

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References

1. Lindell P, Hedenstierna G. Ventilation efficiency after different incisions for cholecystectomy. *Acta Chirurgica Scandinavica* 1976; **142**: 561–565.
2. Ali J, Khan TA. The comparative effects of muscle transection and median upper abdominal incisions on postoperative pulmonary function. *Surgery, Gynecology and Obstetrics* 1979; **148**: 863–866.
3. Brismar B, Pettersson N, Tokics L, Strandberg A, Hedenstierna G. Postoperative analgesia with intrapleural administration of bupivacaine adrenaline. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 515–520.
4. Simonneau G, Vivien A, Sartene R, Kunstlinger F, Sami K, Noviant Y, Duroux P. Diaphragm dysfunction induced by upper abdominal surgery. Role of postoperative pain. *American Review of Respiratory Disease* 1983; **128**: 899–903.

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Influence of motivation of care providers on the incidence of postoperative hypoxaemia in the recovery room†

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Summary

We have studied the influence of motivation of care providers on the incidence and duration of postoperative hypoxaemia in the recovery room. In a prospective, switch-back designed cohort study, we have compared the incidence of low pulse oximeter saturation values (Sp_{O_2}) during pre-intervention, intervention and post-intervention phases. Low Sp_{O_2} values were classified as either hypoxaemia ($Sp_{O_2} \leq 90\%$, minimum duration 1 min) or artefact. Pulse oximetry trend data from 1350 patients, 450 in each group, were analysed. During the intervention phase, motivation was increased by adding an explicit instruction to prevent and treat low Sp_{O_2} values and making personnel aware that they were being studied (Hawthorne effect). The incidence of hypoxaemia decreased significantly from 17.8% during the pre-intervention phase to 11.6% during the intervention phase (relative risk (RR) 0.65, 95% confidence interval (CI) 0.47–0.90; $P<0.01$). The incidence of severe hypoxaemia ($Sp_{O_2} \leq 85\%$, 1 min) decreased from 7.8% to 3.3% (RR 0.43, CI 0.24–0.76; $P<0.01$). The number of patients who had severe hypoxaemia for more than 5 min decreased from 13 to 1 (RR 0.08, CI 0.02–0.36; $P<0.01$). In the post-intervention period, the incidence of hypoxaemia returned to pre-intervention values. The results of this study suggest that motivation of care providers to prevent and treat low Sp_{O_2} is an important determinant of postoperative hypoxaemia in the recovery room. (*Br. J. Anaesth.* 1996;**77**:453–457)

Key words

Hypoxaemia. Surgery, postoperative period. Monitoring, oxygen.

Pulse oximetry is used in the recovery room to alert staff to life-threatening respiratory events and to detect milder forms of hypoxaemia that may require treatment[1–3]. Although the pulse oximeter is highly sensitive for hypoxaemia, its specificity is low. Especially in the early postoperative phase, pulse oximeter artefacts may produce oxyhaemoglobin saturation (Sp_{O_2}) values that do not represent hypoxaemia[4 5]. In a recent study the average frequency of pulse oximeter alarms ($Sp_{O_2} \leq 90\%$) being sounded in the recovery room was once every 8 min, with 77% of alarms being false[6]. We suspected that a very high incidence of false alarms could encourage recovery room nurses to accept low Sp_{O_2} values as "normal" or "inevitable" and decrease their motivation to treat hypoxaemia.

This prospective cohort study was designed to test if motivation of care providers plays a role in preventing hypoxaemia. The study had a switch-back design (pre-intervention, intervention, post-intervention). Care providers (recovery room nurses and anaesthetists) were unaware of Sp_{O_2} data collection in the pre-intervention period. In the intervention period an explicit instruction to maintain $Sp_{O_2}>90\%$ accompanied each patient, and care providers were purposely made aware that they were being studied. The null hypothesis was that the intervention would not change the incidence or duration of hypoxaemia. The post-intervention period served to ascertain if any possible change in the incidence of hypoxaemia occurring during phase 2 persisted after the incentives to prevent and treat low Sp_{O_2} values were removed.

Patients and methods

The study was performed in a 650-bed community hospital. Six full-time anaesthetists (minimum experience 6 yr post-graduation) are on staff. There are 10 operating rooms and a nine-bed recovery room. Neurosurgical procedures or cardiac surgery are not performed. Neither the types of case nor the anaesthetic technique changed over the three study phases. Patients undergoing operations under general, spinal or extradural anaesthesia, who were

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monitored for at least 10 min in the recovery room, were eligible to enter the study. There were no exclusion criteria based on age or clinical condition of the patient.

For each of the three study phases, Sp_{O_2} data from 450 consecutive patients were retrieved from pulse oximeter memory (3–4 weeks for each phase).

During phase 1, anaesthetists and nurses were unaware of Sp_{O_2} data collection. The default lower alarm limit of the pulse oximeter was 90%. There were no specific written guidelines regarding treatment of postoperative hypoxaemia. This study phase was designed to determine the incidence of hypoxaemia during routine postoperative care. After analysis of these data, care providers were informed of the incidence and duration of postoperative hypoxaemia, and the study design was explained. No attempt was made to link hypoxaemia to individual anaesthetists or nurses.

Phase 2 of the study, the intervention period, was conducted immediately after completion of phase 1. An explicit written instruction to maintain $Sp_{O_2}>90\%$ accompanied each patient, but no specific instructions regarding the methods of maintaining normoxaemia were given. Anaesthetists and nurses were now aware that pulse oximetry data from the next 450 patients would be retrieved and analysed. In this way a positive bias on performance, resulting from the knowledge of being studied (Hawthorne effect) was purposely introduced. After completion of phase 2, data were analysed and the results presented to care providers. From that time, the written instruction to prevent hypoxaemia was omitted from the postoperative orders.

Phase 3 started 2 months after completion of phase 2. There was no written instruction to prevent hypoxaemia in the postoperative orders. Anaesthetists and nurses were again unaware that pulse oximetry data were collected.

The hospital Ethics Committee advised that only patients in phase 2 were required to give informed consent, as data obtained in phases 1 and 3 consisted of anonymous pulse oximeter trend data and no randomization was involved.

RECOVERY ROOM AND DATA ACQUISITION

One nurse takes care of a maximum of two postoperative patients at a time. If necessary, postoperative mechanical ventilation is available for two patients. Supplementary oxygen is not administered during transport from the operating theatre to the recovery room. In the recovery room supplementary oxygen is administered by nasal cannula to all patients during the initial postoperative period. The minimum duration of stay for an individual patient is ordered by the responsible anaesthetist at the time of arrival.

Routine pulse oximetry monitoring had been established 4 yr previously. A Criticare 504 pulse oximeter with system software version 3.1 (Criticare Systems, Inc., Waukesha,WI, USA) was used for monitoring Sp_{O_2}. This monitor shows a plethysmographic waveform and does not apply autoscaling. Signal averaging has a default value of 12 s. Monitoring started immediately after arrival of the patient and was continued until the time of discharge. The probe of the pulse oximeter was applied to a finger of the hand opposite to the arterial pressure cuff. The Sp_{O_2} lower alarm limit used at the start of monitoring was 90%. This level was the default lower alarm limit on all oximeters for the past 4 yr. It was chosen to reflect a threshold that would undisputedly suggest a need for therapy. A loud audible alarm sounds when Sp_{O_2} decreases below the lower alarm limit or when the pulse oximeter is unable to measure Sp_{O_2} because of a low signal-to-noise ratio or disconnection of the probe from the finger.

Sp_{O_2} and pulse frequency, together with time, were stored every 5 s in the memory of the pulse oximeter. At the end of the day, when the last patient had been discharged to the ward and personnel had left the recovery room, these data were transferred from pulse oximeter memory to a personal computer for off-line analysis.

DATA ANALYSIS

Individual Sp_{O_2} trend arrays were validated before analysis. Episodes with $Sp_{O_2}\leq 90\%$ were classified as either hypoxaemia or artefact. The algorithm used to exclude episodes with artefact used the following criteria: (1) transient outlier: a single datum point (5-s resolution) changed more than 4% from the surrounding data; (2) low signal-to-noise ratio: loss of signal occurred 20 s before until 20 s after the episode of low Sp_{O_2}; and (3) decrease in Sp_{O_2} of more then 10% within 5 s. Two arbitrary levels of hypoxaemia were defined and for each patient the cumulative duration of hypoxaemia was calculated. Hypoxaemia was defined as episodes of $Sp_{O_2}\leq 90\%$ lasting at least 1 min. Severe hypoxaemia was considered to be present when Sp_{O_2} values were at or below 85% for at least 1 min.

In each study phase the following were determined: number of patients who were hypoxaemic at any moment during pulse oximetry monitoring in the recovery room; number of patients who arrived hypoxaemic in the recovery room; and number of hypoxaemic patients, after excluding data recorded during the first 3 min of monitoring in the recovery room.

STATISTICAL ANALYSIS

Data are presented as counts and percentiles. Differences between phases were analysed using chi-square and Kruskal–Wallis tests. $P<0.05$ was considered significant. Group size was calculated to achieve 85% power to detect a 50% decrease in the incidence of hypoxaemia. The incidence of hypoxaemia during phase 2 was expressed as relative risk to phase 1. The confidence interval for relative risk was calculated using the Mantel–Haenszel chi-square statistic.

Results

Patient data, anaesthesia data and duration of postoperative monitoring are shown in table 1. Median duration of stay in the recovery room in phase 2 was 6 min longer ($P<0.01$).

The audible Sp_{O_2} alarm was triggered 766 times during phase 1 (mean 2.1 times per hour of monitoring), 411 times during phase 2 (1.2 per hour) and

Table 1 Patient data, anaesthesia data and postoperative care. **$P < 0.01$ compared with phase 1, ††$P < 0.01$ compared with phase 2

	Phase 1 (n=450)	Phase 2 (n=450)	Phase 3 (n=450)
Median age (range) (yr)	42 (0–88)	43 (0–91)	42 (0–90)
Sex (M/F)	220/230	222/228	215/235
General anaesthesia (n)	385	391	395
General + regional anaesthesia (n)	21	19	16
Regional anaesthesia (n)	44	40	39
Median duration of anaesthesia (10th–90th percentiles) (min)	44 (10–91)	46 (10–90)	46 (9–92)
Median duration of monitoring (10th–90th percentiles) (min)	37 (14–96)	43** (18–108)	39†† (14–108)

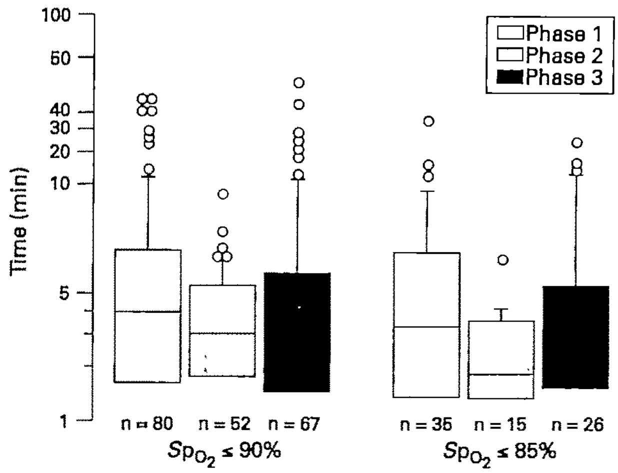

Figure 1 Cumulative duration of hypoxaemia for two thresholds ($Sp_{O_2} \leq 90\%$ and $Sp_{O_2} \leq 85\%$) during the three study phases. Median duration of hypoxaemia was not different between study phases, but the number of patients who were hypoxaemic for more than 5 min was reduced in phase 2. Box plots show medians (horizontal line in box), 25th and 75th percentiles (lower and upper box margins) and 90th percentiles (upper error bar). Open circles=individual patients in the upper 10th percentile. The y-axis has a logarithmic scale in minutes. Below the boxes the absolute numbers of hypoxaemic patients in each study phase are given.

588 times during phase 3 (1.5 per hour). In 53% of patients, the Sp_{O_2} signal was lost transiently at some time during monitoring. There were no differences in the incidence or duration of "no signal conditions" (median duration 40 s) between the three phases of the study. The incidence of artefacts was reduced in phase 2 (table 2).

Table 2 shows the number of hypoxaemic patients in each phase. In phase 1, 17.8% of patients experienced hypoxaemia. During phase 2 it decreased to 11.6% (relative risk (RR) 0.65, 95% confidence interval (CI) 0.47–0.90; P<0.01). More severe hypoxaemia ($Sp_{O_2} \leq 85\%$) was noted at some time in 7.8% of patients during phase 1; in phase 2 it decreased to 3.3% (RR 0.43, CI 0.24–0.76; P<0.01). The reduction in postoperative hypoxaemia during phase 2 was not persistent: the incidence of hypoxaemia in phase 3 was not significantly different from phase 1. The number of patients who arrived hypoxaemic in the recovery room was less in phase 2 compared with phase 1. When data recorded during the first 3 min of monitoring were excluded from analysis, the reduction in hypoxaemia in phase 2 compared with phase 1 remained.

Median duration of hypoxaemia was not different between the three study groups. However, the 90th percentile of the duration of severe hypoxaemia was 19 min in phase 1, 3.5 min in phase 2 and 21 min phase 3 (fig. 1). Severe hypoxaemia lasting more than 5 min occurred in 13 patients during phase 1 compared with in one patient during phase 2, and in six patients during phase 3 (RR 0.08, CI 0.02–0.36; P<0.01).

Discussion

We have found that an explicit instruction to maintain Sp_{O_2}>90%, combined with the knowledge of being studied, may reduce the incidence of postoperative hypoxaemia by as much as 50%. The recurrence of hypoxaemia 4 months after intervention further supports the hypothesis that motivational factors of care providers is an important determinant of the incidence of postoperative

Table 2 Incidence of hypoxaemia and artefacts for two thresholds ($Sp_{O_2} \leq 90\%$, $Sp_{O_2} \leq 85\%$). Only episodes lasting ≥60 s were included in the calculations (absolute number of patients (%)). **$P < 0.01$ compared with phase 1, †$P < 0.05$ compared with phase 2. Relative risk = phase 2 to phase 1 (95% confidence interval (CI))

	Phase 1 (n=450)	Phase 2 (n=450)	Phase 3 (n=450)	Relative risk (CI)
Hypoxaemia ($Sp_{O_2} \leq 90\%$)				
Total No. of hypoxaemic patients (%)	80 (17.8)	52 (11.6)**	67 (14.9)	0.65 (0.47–0.90)
No. of hypoxaemic patients at arrival in the recovery room (%)	14 (3.1)	2 (0.4)**	10 (2.2)†	0.14 (0.04–0.49)
No. of hypoxaemic patients after exclusion of the the first 3 min of monitoring	74 (16.4)	46 (10.2)**	61 (13.6)	0.62 (0.44–0.87)
Severe hypoxaemia ($Sp_{O_2} \leq 85\%$)				
Total No. of hypoxaemic patients (%)	35 (7.8)	15 (3.3)**	26 (5.8)	0.43 (0.24–0.76)
No. of hypoxaemic patients at arrival in the recovery room (%)	2 (0.4)	1 (0.2)	2 (0.4)	0.50 (0.05–5.20)
No. of hypoxaemic patients after exclusion of the the first 3 min of monitoring	34 (7.6)	14 (3.1)**	24 (5.3)	0.41 (0.23–0.74)
Artefacts				
$Sp_{O_2} \leq 90\%$	67 (14.9)	33 (7.3)**	50 (11.1)	0.49 (0.34–0.72)
$Sp_{O_2} \leq 85\%$	36 (8.0)	17 (3.8)**	25 (5.6)	0.47 (0.27–0.82)

hypoxaemia. With this sample size the study lacked sufficient statistical power to determine if some residual effect of the intervention was present in phase 3, and it is possible that a larger study population might have shown such an effect. However, a larger study population would have required a longer data collection period, during which time changes in recovery room personnel could not be avoided.

Subjects who are aware of being studied behave differently, and usually performance increases (Hawthorne effect). In several studies on the incidence of postoperative hypoxaemia, the investigators used bedside observers to record the actions of personnel and to verify that a valid pulse oximeter signal was present[2,3,7]. However, the presence of an observer might introduce a Hawthorne effect and the possibility exists that studies involving direct observation of personnel do not reflect the actual situation during routine postoperative care. The aim of the pre-intervention phase was to document existing practices. Therefore, anaesthetists and nurses were not informed that pulse oximetry data were collected and no observers were present to document patient care. Although this study design precluded matching of pulse oximetry data from individual patients with specific therapeutic interventions, the absence of observers made it possible to document real practice and to introduce a positive study bias during the intervention. No specific instructions regarding particular methods to prevent or treat hypoxaemia were given. In this way we tried to ensure that any change in the incidence of hypoxaemia was the result of an action initiated by an individual anaesthetist or nurse, for example administration of reversal drugs or stimulation of the patient, rather than adherence to a specific set of changed postoperative guidelines.

The positive study bias introduced during phase 2 not only influenced postoperative care, but also altered intraoperative care. Anaesthetists were aware of the ongoing data collection and there was a substantial reduction in the incidence of hypoxaemia on arrival in the recovery room. Anaesthetists may have modified their anaesthetic technique, for example they may have administered a lower dose of opioid which may decrease the incidence of postoperative respiratory depression. Another possible explanation for the reduction in hypoxaemia on arrival might be delayed transport from the operating theatre to the recovery room, with treatment of early hypoxaemia in the operating room rather than in the recovery room. The occurrence of hypoxaemia during transport from the operating to the recovery room has been reported previously[7]. The results of this study showed that increased motivation to prevent hypoxaemia reduced the incidence of hypoxaemia during transportation from 3% to less than 1%.

When the contribution of hypoxaemia on arrival in the recovery room is included in the calculation of the incidence of hypoxaemia during the entire recovery period, it could obscure the possible influence of actions initiated by recovery room nurses. Therefore, we have recalculated the incidence of hypoxaemia after excluding data from the first 3 min after arrival. During these 3 min the effect of supplementary oxygen or stimulation of the patient on Sp_{O_2}, or both, would be expected to become apparent. The reduction in hypoxaemia remained after exclusion of data recorded during the first minutes after arrival, suggesting that both anaesthetists and nurses contributed to the decreased incidence of hypoxaemia.

When pulse oximeter data are not validated by verifying the presence of a plethysmographic signal of sufficient quality, the incidence of hypoxaemia is overestimated because of inclusion of episodes with erroneously low Sp_{O_2} values. In one study 9% of pulse oximetry data obtained during emergence from anaesthesia appeared to be invalid[8]. In other studies, up to 75% of low Sp_{O_2} episodes during postoperative care in the recovery room and ICU were false[5,6]. In this study, we used computer analysis of the individual trend data arrays in an attempt to eliminate artefacts. Extra attention to correct application of the finger probe or successful reduction in patient movement in phase 2 decreased the incidence of artefacts by 50%. None the less, the possibility remains that part of the reduction in hypoxaemia during phase 2 may be attributed to a decrease in the number of non-rejected artefacts; however, if application of the artefact algorithms before analysis of hypoxaemia would be insufficient to eliminate all artefacts (and a large number of artefacts remained), the result would be to dilute the apparent effect of the intervention. Most Sp_{O_2} artefacts in the recovery room are of short duration, and are ignored when a minimum duration criterion is in effect. Pan and Gravenstein found that excluding discrepant data less than 12 s decreased the frequency of artefacts by 63% and less than 30 s by 93%[8]. In this study we chose to exclude low Sp_{O_2} episodes lasting less than 60 s in order to reduce the influence of artefacts and to focus attention on clinically more relevant episodes of hypoxaemia.

When used as a physiological monitor, the pulse oximeter should direct the attention of personnel to patients who are at risk for prolonged hypoxaemia. Severe hypoxaemia lasting more than 5 min occurred significantly less often during phase 2, suggesting that patients who were at risk for prolonged severe hypoxaemia gained specifically from the increased attention to early recognition and treatment of hypoxaemia. We can only speculate why pulse oximetry monitoring did not always result in timely interventions to prevent prolonged hypoxaemia during phase 1. Pulse oximetry has often been introduced in the recovery room without clear guidelines on the type of interventions that are required when low Sp_{O_2} values are present. The frequent occurrence of low Sp_{O_2} values without a direct negative effect on patient outcome may have resulted in complacency. A second explanation might be that some of the low Sp_{O_2} values that reflect true hypoxaemia are incorrectly interpreted as artefact. This study cannot differentiate between the relative contribution of the Hawthorne effect and the impact of the explicit instruction to prevent desaturation. However, in several studies that have shown a reduction in postoperative hypoxaemia by pulse oximetry, personnel were observed continuously and motivated explicitly to reduce hypoxaemia[2,3].

In conclusion, the results of this study suggest that motivation of care providers to prevent and treat low Sp_{O_2} values is an important determinant of the incidence of postoperative hypoxaemia in the recovery room.

References

1. Eichhorn JH. Prevention of intraoperative anesthesia accidents and related severe injury through safety monitoring. *Anesthesiology* 1989; **70**: 572–577.
2. Moller JT, Wittrup M, Johansen SH. Hypoxemia in the postanesthesia care unit: an observer study. *Anesthesiology* 1990; **73**: 890–895.
3. Moller JT, Jensen PF, Johannessen NW, Espersen K. Hypoxaemia is reduced by pulse oximetry monitoring in the operating theatre and in the recovery room. *British Journal of Anaesthesia* 1992; **68**: 146–150.
4. Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology* 1989; **70**: 98–108.
5. Visram AR, Jones RDM, Irwin MG, Bacon-Shone J. Use of two oximeters to investigate a method of movement artefact rejection using photoplethysmographic signals. *British Journal of Anaesthesia* 1994; **72**: 388–392.
6. Wiklund L, Hok B, Stahl K, Jordeby-Jonsson A. Postanesthesia monitoring revisited: frequency of true and false alarms from different monitoring devices. *Journal of Clinical Anesthesia* 1994; **6**: 182–188.
7. Bruns J, Turner E, Kettler D. The incidence of hypoxia in the immediate postoperative period. *Anaesthesist* 1992; **41**: 313–315.
8. Pan PH, Gravenstein N. Intraoperative pulse oximetry: frequency and distribution of discrepant data. *Journal of Clinical Anesthesia* 1994; **6**: 491–495.

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Extradural clonidine combined with sufentanil and 0.0625% bupivacaine for analgesia in labour

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Summary

We have studied the use of clonidine combined with low doses of sufentanil and bupivacaine in 45 parturients requiring extradural analgesia for the first stage of labour, in a double-blind, randomized study. We gave 0.0625% bupivacaine 10 ml containing 1:200 000 adrenaline and sufentanil 10 μg (1 ml) to which was added 0.9% saline, or clonidine 100 or 150 μg (1 ml). We compared the quality (VAS scores) and duration of analgesia, motor block, maternal haemodynamic state (mean arterial pressure and heart rate) and fetal and maternal side effects. Mean duration of anaesthesia was prolonged slightly: 105 (SD 21) min without clonidine, 130 (26) min with clonidine 100 μg ($P<0.05$ *vs* control) and 144 (40) min with clonidine 150 μg ($P<0.01$ *vs* control, ns *vs* 100 μg). There were no differences in VAS scores, onset times, heart rate, ventilatory frequency, motor block, sedation, pruritus or bradycardia between the groups. Analgesia was associated with a reduction in mean arterial pressure with clonidine. However, these adverse side effects were of minor clinical importance regardless of the extradural clonidine dose, except for a high incidence of fetal heart tracing abnormalities when clonidine 150 μg was used. These effects associated with a limited effect on analgesia may curtail the widespread use of clonidine as an adjunct to extradural 0.0625% bupivacaine with sufentanil 10 μg during labour. (*Br. J. Anaesth.* 1996;**77**:458–462)

Key words

Anaesthesia, obstetric. Anaesthetics local, bupivacaine. Anaesthetic techniques, extradural. Analgesics opioid, sufentanil. Pharmacology, clonidine.

Opioids are commonly combined with local anaesthetics to enhance extradural anaesthesia during labour[1 2]. Extradural clonidine, an alpha$_2$ adrenergic receptor agonist, produces analgesia without the motor block associated with high doses or concentrations of local anaesthetics[3] or side effects such as nausea, pruritus and risk of respiratory depression associated with the opioids[4]. Therefore, a combination of clonidine and opioids may be an attractive alternative for analgesia in labour but to date there have been no studies designed to assess the safety and efficacy of clonidine combined with low concentrations (<0.125%) of local anaesthetic during analgesia in labour.

The aim of this study was to evaluate the maternal, fetal and neonatal effects of clonidine 100 or 150 μg administered extradurally in combination with 0.0625% bupivacaine and adrenaline 1:200 000 with sufentanil 10 μg during the first stage of labour.

Patients and methods

The study was approved by the hospital Ethics Committee. After obtaining written consent, we studied 45 women, ASA I or II, with a singleton vertex pregnancy of at least 37 weeks' gestation, who requested extradural analgesia in labóur. A sample size calculation was performed using the Instat computer software package (GraphPad Instat, San Diego, CA, USA). Power analysis showed that a sample size of 15 patients per treatment group should provide 95% power (assuming $\alpha=0.05$) to detect a 30-min difference (SD) in duration of analgesia.

All patients had uncomplicated pregnancies and normal fetal heart tracings. We excluded patients receiving antihypertensive drugs, those with baseline heart rates <55 beat min^{-1} and patients who had already received opioid analgesia during this labour.

Each parturient received i.v. infusion of Ringer's lactate 500 ml over 10 min before induction of extradural anaesthesia and was positioned in the sitting position. The extradural space was cannulated at L2–3 or L3–4 using loss of resistance to saline (5 ml) and 3 cm of catheter was left in place. The parturient was then repositioned to lie with a left lateral tilt.

A double-blind, randomized study design was used. Parturients were allocated randomly according to a list of random numbers into three groups (sealed opaque envelopes). All injectates were prepared by an anaesthetist not involved in data collection.

Each syringe of coded study solution was prepared freshly. Each parturient received a test dose of 2% lignocaine 2 ml with 1:200 000 adrenaline. Five minutes later, each received a 12 ml solution comprising 0.0625% bupivacaine 10 ml with sufentanil 10 μg (1 ml) to which was added clonidine 100 μg, clonidine

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150 μg or 0.9% saline (1 ml). Bupivacaine 0.0625% solutions were prepared by diluting 0.25% solutions, without preservatives, with 0.9% saline and adrenaline was then added (1:200 000). Arterial pressure and heart rate were monitored with a non-invasive monitor (Cardiocap II, Datex, Helsinki) 5, 10, 20, 30, 40, 60, 80, 100 and 120 min after extradural injection, and then every 20 min until the need for an additional extradural anaesthetic injection. When additional analgesia was requested, the study was terminated. Subsequent top-up doses were not standardized, allowing the anaesthetist to use either 0.0625% or 0.125% bupivacaine as necessary.

Motor block (modified Bromage score[5]: 0=ability to move hips, ankles and knees; 1=inability to raise extended leg; 2=inability to flex knee; and 3=inability to flex ankle, foot or knee), sedation (1=wide awake, 2=dozing, 3=asleep, 4=unrousable), cephalic dermatomal level of anaesthesia (cold test), ventilatory frequency and oxyhaemoglobin saturation (pulse oximeter, Cardiocap II, Datex, Helsinki) were recorded at the same times. Basal values were those obtained immediately before extradural injection.

Pain was assessed on a linear visual analogue scale (VAS). Each patient was presented with a line 100 mm long and was told that the left end represented no pain and the right end the worst pain imaginable. They were asked to make a mark on the line to indicate the intensity of pain at the peak of a contraction. Patients could request additional analgesia (0.25% bupivacaine via the extradural catheter) if pain relief was unsatisfactory by 15 min after injection of the study drug. At the end of the study, both the patient and nurse made an overall global rating of the treatment (poor, fair, good, very good, excellent).

The time from administration of study drug to request for additional analgesia was noted (duration of analgesia). Side effects such as pruritus, nausea and vomiting were recorded at completion of the study. Bradycardia was defined as the occurrence of a maternal heart rate >60 beat min^{-1} and treated with atropine i.v. Hypotension, defined as a decrease in systolic arterial pressure of at least 20% or a systolic arterial pressure <100 mm Hg, was treated with i.v. ephedrine as necessary.

Continuous electronic cardiotocograph monitoring using an external transducer was used for all patients throughout labour (Hewlett Packard 80034 A). Tracings were analysed by an obstetrician who was unaware of which solution was being administered (F. G.). Analysis compared tracings obtained 30 min before extradural injection with those recorded during analgesia. Changes in baseline fetal heart rate (FHR) (during the interval between uterine contractions), long-term variability (normal pattern >5 beat min^{-1}) and number of tracings with accelerations, early and late decelerations were noted. Variable decelerations were ranked on a scale using the method described by Klavan, Laver and Boscola[6] (mild=decelerations whose nadir >80 beat min^{-1}; moderate=nadir <70 beat min^{-1}, duration between 30 and 60 s or nadir between 70 and 80 beat min^{-1} and duration >60 s; severe=nadir <70 beat min^{-1}, duration >60 s).

Mode of delivery and Apgar scores at 1 and 5 min were recorded. All neonates were examined (general and neurological examinations) 2 h after delivery by a paediatrician who was unaware of patient group assignment.

STATISTICAL METHODS

For all calculations, the Instat computer software package (GraphPad Instat, San Diego, CA, USA) and Solo statistical software (BMDP, Los Angeles, CA, USA) were used. Intragroup comparisons for continuous variables and VAS scores were performed by analysis of variance (ANOVA) for repeated measures, followed by *post hoc* tests for comparison with baseline (Student–Newman–Keuls multiple comparison test). Significance of differences between groups was tested by analysis of variance for repeated measures (ANOVA). The Mann–Whitney *U* test was also used for comparison between groups when necessary (loss of subjects in group A after 100 min).To compare the duration of analgesia we used product limit survival analysis (Kaplan–Meier analysis) followed by Wilcoxon' s test. Where appropriate, Fisher's exact test was performed. Results are expressed as mean (SD).

Results

The groups were comparable in age, weight at term, weeks of pregnancy, parity, VAS pain scores and stage of cervical dilatation at the time of entry into the study (table 1). All patients enrolled in the study were included in data analysis.

Onset times for analgesia did not differ between groups: 6 (2), 6 (2) and 7 (3) min, respectively, for the control and clonidine 100 μg and 150 μg groups. Mean duration of anaesthesia was 105 (21) min (range 70–140 min) for patients who did not receive clonidine, and 130 (26) min (range 100–185 min) (*P*<0.05 *vs* control) and 144 (40) min (range 100–230 min; *P*<0.01 *vs* control, ns *vs* clonidine 100 μg) for patients who received clonidine 100 μg and 150 μg, respectively. The percentage of patients not requesting additional analgesia was greater in the bupivacaine–clonidine 150 μg than in the other

Table 1 Patient data and details of labour (mean (SD or range) or number of patients)

	Control group (*n*=15)	Clonidine 100 μg (*n*=15)	Clonidine 150 μg (*n*=15)
Age (yr)	28 (21–38)	25 (20–31)	26 (20–37)
Weight at term (kg)	73 (11)	72 (13)	69 (8)
Height (cm)	164 (6)	165 (5)	163 (5)
Parity (n)			
0	10	11	9
1	5	4	6
Cervical dilatation at time of study drug (cm)	3.4 (0.9)	3.2 (0.9)	3.2 (0.9)
VAS pain score at time of study drug	6.14 (1.83)	6.53 (2.02)	6.83 (1.97)
Gestation (weeks)	39 (1.6)	39 (1)	39 (1.5)
Sensory level at 5 min (median (range))	T10 (6–12)	T10 (9–12)	T10 (6–12)
Spontaneous delivery	13	11	12
Instrumental delivery	2	2	1
Caesarean section	0	2	2

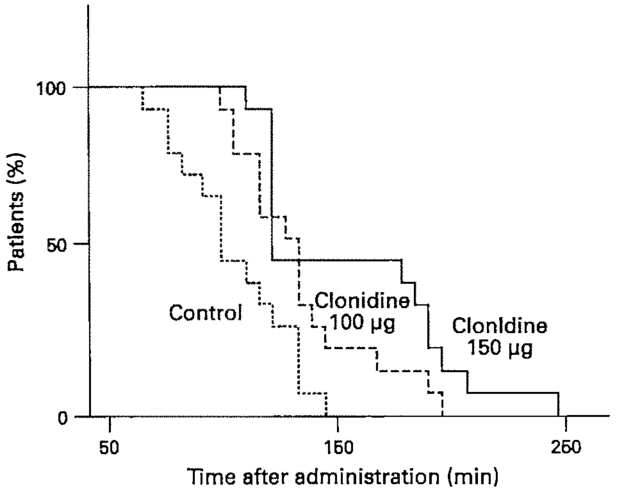

Figure 1 Percentage of patients not requesting additional analgesia after extradural injection of 0.0625% bupivacaine and sufentanil with saline (control) or clonidine 100 µg or 150 µg (50th percentiles for the three groups were: 100 min for the control group, 120 min for the clonidine 100 µg group and 127 min for the clonidine 150 µg group).

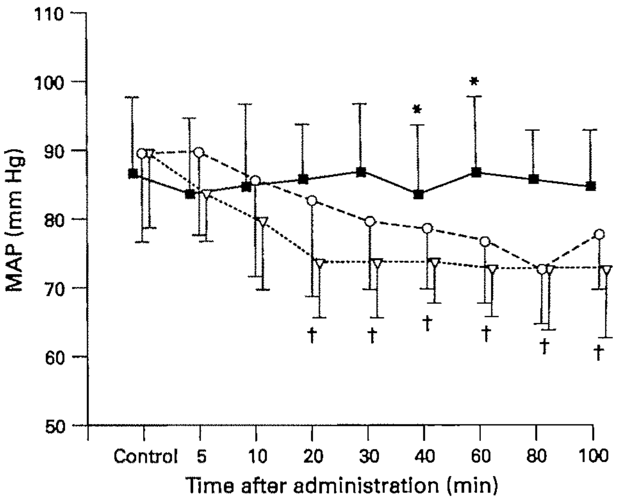

Figure 2 Mean arterial pressure (MAP) before (Control) and after extradural injection of 0.0625% bupivacaine and sufentanil with saline (■), clonidine 100 µg (○) or clonidine 150 µg (▽). *$P<0.05$ clonidine 150 µg *vs* control group; †$P<0.05$ clonidine 100 µg *vs* control group.

groups when analysed by Kaplan–Meier survival analysis followed by Wilcoxon's test (fig.1). No patient failed to achieve analgesia throughout the study in both groups. Mean VAS scores decreased significantly within 5 min after administration of drug. By 80 min, although both clonidine groups had lower pain scores than the control group, this was not statistically significant until 100 min (table 2). At 100 and 120 min, pain scores between groups 100 and 150 µg were not significantly different. Overall, the degree of maternal and nurse satisfaction was high in all groups.

Maternal heart rates were comparable in all three groups before administration of the study drug: 85 (14) beat min^{-1} for the control group, 82 (12) beat min^{-1} for the clonidine 100 µg group and 86 (11) beat min^{-1} for the clonidine 150 µg group. Atropine was administered for bradycardia in one patient in the clonidine 150 µg group.

Mean arterial pressure (MAP) was comparable in all groups at baseline: 87 (10), 90 (13) and 89 (10) mm Hg, respectively. From baseline to time 120 min, there were no significant changes in MAP in the control group, whereas it decreased significantly at 20 min in the clonidine 100 µg group (82 (14) mm Hg; $P<0.05$) (fig. 2). From 20 to 140 min this decrease remained significant, being highly significant at 40 min (79 (8) mm Hg; $P<0.001$). In the clonidine 150 µg group, MAP decreased more rapidly (at 5 min: 83 (6) mm Hg; $P<0.05$) and was highly significant at 20 min (73 (8) mm Hg; $P<0.001$). In all three groups, MAP was not different over the first 20 min (fig. 2).

One patient in the control group, two in the clonidine 100 µg group and one in the clonidine 150 µg group needed ephedrine for transient hypotension (ns).

There was no change in Sp_{O_2} at any time. Basal ventilatory frequency was comparable between groups and no significant change was noted throughout the study in the control and clonidine 100 µg group. In the clonidine 150 µg group, there was a significant decrease in ventilatory frequency in the first 80 min: 17 (5) bpm at 40 min *vs* 21 (3) bpm at baseline ($P<0.01$). However, inter-group comparisons showed no significant differences over the first 100 min.

In the control group, no patient had a Bromage score exceeding 1. Only one patient in each of the clonidine groups had a score of 2; no patient had Bromage score 3. Sedation scores were comparable between groups. No patient in the control group, one in the clonidine 100 µg group and two in the clonidine 150 µg group had a sedation score of 3.

Differences in FHR patterns were noted between groups. A decrease in long-term variability ($P<0.04$) and bradycardia (FHR <120 beat min^{-1}) were more usual in the clonidine 150 µg group ($P<0.02$). The numbers of tracings with variable ($P<0.01$) and late decelerations ($P<0.04$) were significantly more frequent in the clonidine 150 µg group, while early decelerations were more frequent in the clonidine 100 µg group. For variable decelerations, five were moderate and two mild in the clonidine 150 µg group, four mild and one moderate in the clonidine 100 µg group and three moderate and one mild in the

Table 2 Mean (SD) VAS pain scores for the three groups. **$P<0.01$, ***$P<0.001$ vs control group

	Time (min)									
	0	5	10	20	30	40	60	80	100	120
Control group	6.14	1.6	0.46	0.23	0.16	0	0	1.27	3.85	
(n=15)	(1.83)	(1.76)	(1.12)	(0.77)	(0.44)			(2.10)	(2.28)	
Clonidine 100 µg	6.53	1.5	0.33	0.23	0.06	< 0.1	< 0.1	0.16	1.26	2.20
(n=15)	(2.02)	(1.15)	(0.89)	(0.62)	(0.25)			(0.52)	(1.79)**	(2.28)
Clonidine 150 µg	6.83	1.9	0.8	0.13	< 0.1	< 0.1	< 0.1	0.26	0.53	1.83
(n=15)	(1.97)	(2.65)	(1.78)	(0.51)				(0.79)	(0.82)***	(2.12)

Table 3 Side effects and sedation scores (number of patients). Sedation scores were those recorded 80 min after extradural injection

	Control group (n=15)	Clonidine 100 μg (n=15)	Clonidine 150 μg (n=15)
Pruritus	0	1	0
Nausea	0	1	1
Patients requiring ephedrine	1	2	1
Patients requiring atropine	0	0	1
Sedation score 1 (awake)	0	0	0
Sedation score 2 (dozing)	15	14	13
Sedation score 3 (asleep)	0	1	2

control group. However, no deceleration was classified as severe or needed emergency treatment.

The incidence of side effects was low (table 3). Thirteen patients in the control group had spontaneous vaginal delivery compared with 11 in the clonidine 100 μg group and 12 in the clonidine 150 μg group (table 1). Neonatal Apgar scores at 1 and 5 min did not differ between groups and neurological assessments were normal for all babies at 2 h.

Discussion

Local anaesthetics given extradurally are used widely for analgesia in labour. Fentanyl[7 8] and sufentanil[9] are frequently added to local anaesthetic solutions to potentiate their analgesic effects, allowing a reduced local anaesthetic concentration with less motor block[10–12]. However, the risk of delayed respiratory depression, pruritus and vomiting limits the use of opioids during labour[4]. These adverse effects have stimulated the search for alternative drugs[13] or methods[14] to provide analgesia during labour. We speculated that extradural clonidine, an alpha$_2$ agonist, might provide effective analgesia when combined with sufentanil and low-dose bupivacaine. Extradurally administered clonidine may be ideally suited for obstetric use because it does not interfere with proprioception and does not induce motor block or respiratory depression[15 16].

After extradural administration, clonidine 300 μg alone has been demonstrated to have no effect on fetal physiological indices in sheep[13]. Few studies have assessed the combination of clonidine and local anaesthetics in humans during labour. Brichant and colleagues found that clonidine 75 μg was the optimal dose to add to 10 ml of 0.125% bupivacaine, providing a duration of analgesia of 110 min[17]. Compared with 0.125% bupivacaine alone, clonidine 120 μg combined with 0.125% bupivacaine increased the mean duration of analgesia from 53 to 110 min; analgesia was unsatisfactory in 15% of the clonidine–bupivacaine group compared with 59% in the bupivacaine group[18]. In contrast, a low dose of extradural clonidine (less than 30 μg) failed to increase the duration of analgesia of a sufentanil 10 μg–0.125% bupivacaine mixture[19] or of 0.125% bupivacaine alone[17], while Celleno and colleagues[20] showed considerably prolonged analgesia when clonidine 75 μg was added to fentanyl 100 μg–0.125% bupivacaine (177 *vs* 89 min). The mean duration of analgesia obtained in our study was approximately 130–140 min, longer than that observed with 0.125% bupivacaine and clonidine alone[17 18]. Our results showed that clonidine 100 and 150 μg with a sufentanil 10 μg–0.0625% bupivacaine–adrenaline solution significantly improved the duration of analgesia in the first stage of labour.

Analgesia in the control group was satisfactory without any significant change in MAP. Addition of clonidine 100 or 150 μg prolonged analgesia but caused significant haemodynamic changes. Comparisons between groups showed that this decrease was more important in the clonidine 150 μg group than in the clonidine 100 μg group. Extradural clonidine 700 μg alone decreased arterial pressure and heart rate in volunteers[15] while minor changes in haemodynamic state were reported with extradural clonidine during pregnancy in a sheep model[3]. Doses of clonidine 30–150 μg did not alter haemodynamic state when combined with 0.125% bupivacaine during labour[17 18] and the addition of sufentanil 10 μg[19] or fentanyl 50 μg[20] to clonidine (30 and 75 μg, respectively)–0.125% bupivacaine mixtures did not increase the need for ephedrine treatment during labour. Hypotension during extradural anaesthesia is greater after adrenaline–local anaesthetic solutions than after free adrenaline solution[21]. Extradurally administered clonidine has a U-shaped dose–response for arterial pressure[15] and may explain the decrease in MAP in our study. Although we observed a decrease in MAP, the change in MAP was modest and the incidence of ephedrine treatment was similar in all groups.

While extradural administration of opioids is associated with respiratory depression[4], extradural clonidine did not appear to have a marked effect on ventilation. It has been reported that clonidine does not potentiate morphine or alfentanil-induced respiratory depression[22 23]. In this study, although clonidine was combined with sufentanil, no episode of desaturation was noted and ventilatory frequencies did not differ between groups.

An additional side effect of extradural clonidine is sedation[21]. The incidence of sedation was similar between groups in our study. Other side effects were of minor importance.

Approximately 20% of normal gravidas develop fetal heart rate patterns which place the fetus “at risk” during labour. Most frequently, these patterns occur as a result of either umbilical, maternal or uteroplacental circulatory problems[6]. FHR abnormalities such as variable or late decelerations, bradycardia or change in baseline variability may occur. In this study we found that extradural clonidine, particularly clonidine 150 μg, was associated with such FHR abnormalities. It is unclear at present if these changes were caused by a direct effect of clonidine on the cardiovascular system of the fetus or an effect on oxygen supply. It has been reported that extradural clonidine 150 μg induced serum clonidine concentrations close to 1 ng ml-1 in postoperative patients[24]. In pregnant sheep, clonidine 1 ng ml^{-1} did not decrease uterine blood flow[13] but a direct effect of such concentrations on fetal and uterine blood flow has not been evaluated in labouring parturients. In contrast, a decrease in long-term variability and bradycardia are expected responses after administration of tranquillizers, clonidine, opioids and extradural local anaesthetics[25 26]. In addition, our clinical study contrasts with those of Cellano and colleagues and O' Meara and Gin who showed no effect of clonidine 150 or 120 µg on FHR when given extradurally[18 20]. These differences could be attributed to the different time course of analgesia for the three groups which made intergroup comparisons difficult and to an additional effect of sufentanil on FHR.

References

1. Phillips GH. Extradural sufentanil–bupivacaine combinations for analgesia during labour: effect of varying sufentanil doses. *Anesthesiology* 1987; **67**: 835–838.
2. Cohen SE, Tan S, Albright GA, Halpern J. Extradural fentanyl/bupivacaine mixtures for obstetric analgesia. *Anesthesiology* 1987; **76**: 463–476.
3. Eisenach JC, Dewan DM, Rose JC, Angelo JM. Extradural clonidine produces antinociception but no hypotension in sheep. *Anesthesiology* 1987; **66**: 496–501.
4. Cousins MJ. Intrathecal and extradural administration of opioids. *Anesthesiology* 1984; **61**: 275–310.
5. Bromage PR, Burfort MF, Crowell DE, Pettitgrew RT. Quality of extradural blockade: I. Influence of physical factors. *British Journal of Anaesthesia* 1964; **36** : 342–352.
6. Klavan M, Laver AT, Boscola MA. *Clinical Concepts of Fetal Heart Rate Monitoring*. Waltham, MA: Hewlett Packard, 1977.
7. Chestnut DH, Laszewski LJ, Pollack KL, Bates JN, Manago NK, Choi WW. Continuous extradural infusion of 0.0625% bupivacaine/0.0002% fentanyl during the second stage of labor. *Anesthesiology* 1990; **72**: 613–618.
8. Elliot RD. Continuous infusion extradural analgesia for obstetrics: bupivacaine versus bupivacaine fentanyl mixture. *Canadian Journal of Anaesthesia* 1991; **38**: 303–310.
9. Steinberg RB, Dunn SM, Dixon DE, Rehn KL, Pastides H, Xu X. Comparison of sufentanil, bupivacaine, and their combination for extradural analgesia in obstetrics. *Regional Anesthesia* 1992; **17**: 225–228.
10. Chestnut DH, Owen CL, Bates JN, Ostman LG, Choi WW, Geiger MW. Continuous infusion of extradural analgesia during labor: a randomized, double-blind comparison of 0.0625% bupivacaine/0.0002% fentanyl versus 0.125% bupivacaine. *Anesthesiology* 1988; **68**: 754–759.
11. Li DF, Rees AD, Rosen M. Continuous extradural infusion of 0.0625% or 0.125% bupivacaine for pain relief in primigravid labour. *British Journal of Anaesthesia* 1985 ; **57**: 264–270.
12. Stoddart AP, Nicholson KEA, Popham PA. Low dose bupivacaine/fentanyl extradural infusions in labour and mode of delivery. *Anaesthesia* 1994; **49**: 1087–1090.
13. Eisenach JC, Castro MI, Dewan DM, Rose JC. Extradural clonidine analgesia in obstetrics: sheep studies. *Anesthesiology* 1989; **70**: 51–56.
14. Leighton BL, DeSimone CA, Norris MC, Ben-David B. Intrathecal narcotics for labor revisited: The combination of fentanyl and morphine intrathecally provides profound, prolonged analgesia. *Anesthesia and Analgesia* 1989; **69**: 122–125.
15. Eisenach J, Detweiler D, Hood D. Hemodynamic and analgesic actions of epidurally administered clonidine. *Anesthesiology* 1993; **78**: 277–287.
16. Buggy DJ, Mac Dowell C. Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour. *British Journal of Anaesthesia* 1996; **76** : 319–321.
17. Brichant JF, Bonhomme V, Mikulski M, Lamy M, Hans P. Admixture of clonidine to extradural bupivacaine for analgesia during labor: effect of varying clonidine doses. *Anesthesiology* 1994; **81**: A 1136.
18. O' Meara ME, Gin T. Comparison of 0.125% bupivacaine with 0.125% bupivacaine and clonidine as extradural analgesia in the first stage of labour. *British Journal of Anaesthesia* 1993; **71**: 651–656.
19. Le Polain B, De Kock M, Scholtes JL, Van Lierde M. Clonidine combined with sufentanil and bupivacaine with adrenaline for obstetric analgesia. *British Journal of Anaesthesia* 1993; **71**: 657–660.
20. Celleno D, Capogna G, Costantino P, Zangrillo A. comparison of fentanyl with clonidine as adjuvants for extradural analgesia with 0.125% bupivacaine in the first stage of labor. *International Journal of Obstetric Anesthesia* 1995; **4**: 26–29.
21. Nishikawa T, Dohi S. Clinical evalutation of clonidine added to lidocaine solution for extradural anesthesia. *Anesthesiology* 1990; **73**: 853–859.
22. Bailey PL, Sperry RJ, Johnson GK, Eldredge SJ, East TH, Pace NL, Stanley TH. Respiratory effect of clonidine alone and combined with morphine in humans. *Anesthesiology* 1991; **74**: 43–48.
23. Javis DA, Duncan SR, Segal IS, Maze M. Ventilatory effects of clonidine alone and in the presence of alfentanil, in humans volunteers. *Anesthesiology* 1992; **76**: 899–905.
24. Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M. Clonidine-induced analgesia in postoperative patients: extradural *versus* intramuscular administration. *Anesthesiology* 1990; **72**: 423–427.
25. Lavin JP, Samuels SV, Miodovnik M, Holroyde J, Loom M, Joyce C. The effects of bupivacaine and chloroprocaine as local anesthetics for extradural anesthesia on fetal heart rate monitoring parameters. *American Journal of Obstetrics and Gynecology* 1981 ; **141**: 717–722.
26. Abboud TK, Afrasiabi A, Sarkis F, Daftarian F, Naggapala S, Noueihed R, Kunhert RR, Miller F. Continuous infusion extradural analgesia in parturients receiving bupivacaine, chloroprocaine or lidocaine. *Anesthesia and Analgesia* 1984; **63**: 421–428.

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Antiemetic effect of subhypnotic doses of propofol after thyroidectomy†

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Summary

Postoperative nausea and vomiting (PONV) are unpleasant, often underestimated side effects of anaesthesia and surgery, not devoid of medical complications. Prevention with antiemetics is only partially effective. Propofol has been shown recently to possess antiemetic properties in several situations. In this prospective, randomized, controlled trial, we have compared the antiemetic efficacy of subhypnotic doses of propofol, with Intralipid as placebo, after thyroidectomy. We studied 64 patients of both sexes, aged 22–71 yr, ASA I or II, undergoing thyroidectomy. After premedication with a benzodiazepine, balanced anaesthesia was produced with isoflurane and nitrous oxide in oxygen, and supplementary analgesia with fentanyl i.v. as required. Postoperative analgesia was provided with non-opioids, and piritramide 0.25 mg kg^{-1} i.m. on demand. Patients were allocated randomly and blindly to receive a 20-h infusion of either propofol or 10% Intralipid 0.1 ml kg^{-1} h^{-1}. Intralipid, the excipient of propofol, was chosen as placebo as it is devoid of antiemetic effects. Sedation scores, respiratory and cardiovascular variables, and incidence of PONV were assessed every 4 h for 24 h. Pulse oximetry and ECG were monitored continuously. Both groups were comparable in characteristics, surgical and anaesthesia procedures, amount of opioids given during and after operation, and total amount of the study drug infused after operation. Occurrence of PONV was similar before the start (propofol 41%, Intralipid 50%) and after completion (propofol 0.64%, Intralipid 1.6%) of infusion and decreased with time in both groups during the infusion. However, symptoms were reduced to nil with propofol but persisted and were more severe with Intralipid during infusion ($P \le 0.01$). The overall incidence of PONV during infusion was 10% (three of 32 patients) in the propofol group and 65% (21 of 32 patients) in the Intralipid group. Cardiovascular and respiratory variables, and Sp_{O_2} were unaltered, and sedation decreased similarly with time in both groups. We conclude that propofol, given at subhypnotic doses, effectively reduced the incidence of PONV without untoward sedative or cardiovascular effects. (*Br. J. Anaesth.* 1996;**77**:463–467)

Key words

Vomiting, nausea. Vomiting, nausea, anaesthetic factors. Anaesthetics i.v., propofol. Surgery, thyroidectomy.

Postoperative nausea and vomiting (PONV) are common, often neglected side effects of surgery. Their incidence has been estimated, in multicentre studies, to be as high as 40–60%[1]. Apart from the distressing inconvenience, the muscular efforts accompanying these symptoms may contribute to medical complications such as aspiration pneumonia, wound dehiscence, bleeding and even wound infection[2]. Thyroidectomy is associated with a high rate of PONV and prevention with antiemetics such as metoclopramide or alizapride reduces their frequency from 60% to only approximately 40%[3].

Propofol has been associated with a reduced rate of PONV when used as a continuous infusion to provide anaesthesia[4–9]. This advantage is limited to the early postoperative period, up to 6 h after completion of surgery[8]. In contrast, propofol has been used successfully at subhypnotic doses (0.5–1 mg kg^{-1} h^{-1}) for the prevention and treatment of chemotherapy-induced emesis[10 11] and after surgery[12 13].

We have evaluated, in a randomized, prospective study, the antiemetic properties of propofol infused continuously at subhypnotic doses compared with a placebo, in thyroidectomized patients. Intralipid 10% was chosen as placebo as, being the excipient of propofol, it is indistinguishable from the drug and has proved to be devoid of antiemetic and emetogenic effects[14].

Patients and methods

After obtaining institutional approval from the Ethics Committee, we studied 66 patients of both sexes, ASA I–II, aged 22–71 yr, undergoing thyroidectomy. Patients with allergy or intolerance to any of the products to be used during or after operation, or those receiving neuroleptics, were excluded. All patients gave informed consent before participation and were allocated randomly to receive either propofol or placebo after operation.

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The anaesthetic procedure was the same for all patients. Premedication comprised midazolam i.m., 30 min before induction of anaesthesia. Oral diazepam, 60 min before induction, was given to a few patients reluctant to have an injection. In the operating theatre, patients received an i.v. balanced electrolytic solution (Plasmalyte, Travenol, Baxter) via a peripheral vein and standard monitoring was commenced (ECG lead II, heart rate, automatic arterial pressure, pulse oximetry). Anaesthesia was induced with fentanyl 2 μg kg^{-1} i.v. and thiopentone 3–5 mg kg^{-1} i.v. A single dose of atracurium 0.4–0.5 mg kg^{-1} was used to facilitate tracheal intubation and neuromuscular block was not used thereafter. After tracheal intubation with a cuffed armoured tube, anaesthesia was maintained with 0.5–2% isoflurane and 60–70% nitrous oxide in oxygen administered via a respirator. Ventilatory variables and respiratory gases were monitored conventionally. Supplementary analgesia during surgery was provided with boluses of fentanyl 50–100 μg i.v.

At the end of operation, after tracheal extubation, patients were transferred to the surgical intensive care unit for 24 h. Postoperative monitoring was standard and comprised ECG, pulse oximetry and regular assessment of conscious status, arterial pressure, ventilatory frequency and fluid balance. Analgesia consisted of intra-rectal administration of indomethacin 100 mg twice daily or propacetamol 1 g i.v. every 4 h, or both. If inadequate, additional doses of piritramide (Dipidolor, Janssen Pharmaceutica) 0.1–0.25 mg kg^{-1} i.m. were given at the request of the patient at a maximum frequency of every 4 h.

When patients were considered sufficiently oriented by the nursing staff, an infusion of propofol or 10% Intralipid, prepared and provided according to the randomization schedule, was started at a rate of 0.1 ml kg^{-1} h^{-1} via a syringe pump.

Factors contributing to PONV, such as clinical status (euthyroidism, hyperthyroidism treated or not), previous history of PONV, date of last menses for women, duration of anaesthetic and surgical procedure, occurrence of hypotension during anaesthesia (defined as a decrease in systolic arterial pressure of more than 20% from baseline), difficulty of tracheal intubation (graded as easy, moderately difficult, difficult) and administration of opioid analgesia were recorded in order to assess the comparability of the two groups.

During the whole infusion period, the incidence and severity of PONV and eventual side effects were assessed as follows: every 4 h, patients were questioned and asked if they had experienced nausea and vomiting during the preceding period; in addition, any episode occurring outside the observation time and not self-reported was taken into account and noted. As the observation lasted at least 24 h, the assessment could not be made by only one investigator, but was made by trained nurses and controlled subsequently by the chief nurse (C. W.) and another investigator, preferentially always the same (S. J.). Nausea and vomiting were assessed using the score of Bellville[15]: 0=no symptoms; 1=nausea (subjective unpleasant sensation with awareness of urge to vomit); 2=retching (spasmodic contractions of abdominal wall and diaphragmatic muscles without expulsion of gastric content); 3=vomiting (same as (2) but with forceful expulsion of gastric contents). Whenever symptoms occurred, metoclopramide 10 mg i.v. was given as rescue drug, every 4 h if necessary.

Sedation was evaluated simultaneously using a four-point rating scale[10]. A score of 1 (patient fully awake) or 2 (patient sleepy, but rousable by verbal stimulation) was considered adequate. If the sedation score reached 3 (sleepy, not responding to verbal, but well to painful stimulation), the infusion rate of the study drug was reduced by half and stopped if the score was 4 (not rousable, not responding to painful stimulation).

Pain and satisfaction scores were also assessed after 10 and 20 h of infusion of the study drug, using a visual analogue scale (VAS) from 0 (no pain) to 10 (worst conceivable pain). During the night, if the patient was found quietly asleep, he/she was not awakened and only monitoring signs were noted. At the end of the infusion period, patients were observed for an extra 4-h period to assess evolution of PONV.

STATISTICAL ANALYSIS

Parametric data were submitted to analysis of variance. When the F ratio reached statistical significance, a t test (two-sided unpaired Student's test or two-tailed Fisher's exact test) was applied. Non-parametric data were analysed where applicable by the chi-square or Wilcoxon rank sum test. $P \leq 0.05$ was considered statistically significant.

Results

There were 32 patients in each group. Sex distribution, age, weight, height and ASA status were comparable. There was no difference in clinical status or other preoperative factors predisposing to PONV. Duration of anaesthesia and surgery, intubation difficulty, hypotensive episodes, and peroperative use of fentanyl were similar in both groups (table 1).

Patients received the same amount of propofol or Intralipid at the same rate and during the same period. Infusion of the study drug was started at the same time in both groups (with a median time of 30

Table 1 Patient data and predisposing factors (mean (SEM or range) or number. No significant differences between groups

	Propofol group (n=32)	Intralipid group (n=32)
Age (yr)	44 (22–60)	44 (23–71)
Sex (F/M)	26/6	31/1
Weight (kg)	67 (13)	67 (11)
Height (cm)	167 (9)	164 (7)
ASA status I/II	17/15	17/15
History of PONV (no/yes)	19/8	18/10
Hypotensive episodes (no/yes)	26/3	29/2
Difficult intubation (easy/moderate/difficult)	25/3/2	27/4/0
Preoperative fentanyl total dose (μg)	418 (18)	436 (26)
Anaesthesia duration (min)	162 (5)	165 (8)
Surgery duration (min)	122 (5)	123 (8)

Table 2 Trial drug infusion data (mean (SEM), median (range) or number). No significant differences between groups

	Propofol group	Intralipid group
Time from extubation until start of infusion (min)	30 (5–270)	35 (10–180)
Infusion rate (ml kg^{-1} h^{-1})	6.8 (0.2)	6.7 (0.2)
Total amount infused (ml)	130 (4.5)	125 (4.5)
Rate change (*n*) (no/half/stopped)	30/2/0	27/5/0

min in the propofol group and 35 min in the Intralipid group) after the end of operation. The infusion rate was reduced by the nurses twice in the propofol group and five times in the Intralipid group (ns) because of a sedation score of 2 after 8 h of perfusion (although this was considered acceptable in the study design) (table 2).

Table 3 Incidence of symptoms during observation period (number of patients (%))

	Propofol group	Intralipid group	*P*
Before infusion			
No symptoms	19 (59)	16 (50)	
Nausea	3	6	ns
Retching	1	2	
Vomiting	9	8	
0–4 h			
No symptoms	30 (94)	22 (73)	
Nausea	0	3	0.0134
Retching	0	0	
Vomiting	2	7	
4–8 h			
No symptoms	31 (97)	19 (59)	
Nausea	1	3	0.0004
Retching	0	0	
Vomiting	0	9	
8–12 h			
No symptoms	32 (100)	25 (78)	
Nausea	0	0	0.0099
Retching	0	3	
Vomiting	0	3	
12–20 h			
No symptoms	32 (100)	28 (88)	
Nausea	0	2	0.037
Retching	0	0	
Vomiting	0	2	
After infusion			
No symptoms	29 (90)	25 (78)	
Nausea	1	3	ns
Retching	0	0	
Vomiting	1	2	
No. of emetic episodes during observation period (pre-, per- and post-infusion)			
1	10	10	
2	4	13	
3	0	1	
4	0	2	
5	0	1	
Total number of patients with PONV			
Global	14 (44)	27 (84)	< 0.05
Pre-infusion	13 (41)	16 (50)	ns
During infusion	3 (10)	21 (65)	< 0.01
After infusion	2 (6)	5 (15)	ns

Table 4 Concomitant medication (metoclopramide and piritramide) (number of patients)

	Propofol group	Intralipid group	*P*
Metoclopramide			
None	21	10	< 0.01
1 dose	8 (7 pre-infusion)	12 (7 pre-infusion)	ns
2 doses	1	8	< 0.05
3 doses	0	1	—
Piritramide			
None	22	17	ns
1 dose	8	9	ns
2 doses	0	2	ns
3 doses	0	1	ns

Before the start of infusion of the study drug, PONV had occurred in 45% of patients: 13 of 32 (41%) patients in the propofol group and 16 of 32 (50%) patients in the Intralipid group (ns). During the first period, two patients were still symptomatic (one nauseous, one vomiting) in the propofol group compared with 10 (three nauseous, seven vomiting) in the Intralipid group. One patient was slightly nauseous during the second period, and then the incidence decreased to nil in the propofol group during the rest of the infusion. PONV decreased with time in the Intralipid group but persisted during the whole infusion period. Repeated symptoms were more frequent in the Intralipid group. The differences were statistically significant throughout infusion. After cessation of infusion, PONV was observed in two (6%) patients (one relapse, one nausea "de novo") in the propofol group, compared with five (15%) in the Intralipid group (ns). The overall number of patients with PONV during the whole observation period in the propofol group was 14 (44%) and 27 (84%) in the Intralipid group ($P<0.05$). When only the infusion period was considered, there was a total of three (10%) symptomatic patients in the propofol group P compared with 21 (65%) in the Intralipid group ($P<0.01$) (table 3).

Slight sedation (sedation score of 2) was observed equally in both groups, particularly during the immediate postoperative period and decreased with time in a similar manner. There was no statistically significant difference either in the amount of opioid received (table 4) or the degree of sedation (table 5) at any time. After 10 h of infusion, the median VAS pain score was 0 (range 0–3) in the propofol group and 2 (range 0–6) in the Intralipid group; at 20 h the values were 0 (0–3) and 1 (0–6), respectively. These

Table 5 Sedation score (SS) during infusion (number of patients). No significant differences between groups

	Propofol		Intralipid	
	SS = 1	SS = 2	SS = 1	SS = 2
0–4 h	17	15	18	14
4–8 h	23	9	27	3
8–12 h	26	6	27	4
12–20 h	27	5	26	4

slight differences were not significant. There were no differences between groups in cardiovascular variables and Sp_{O_2} which remained within the normal range throughout the 24 h of observation.

Discussion

We have found that in thyroidectomized patients, PONV was very common, and that propofol, at subhypnotic doses, was effective in comparison with placebo in controlling the incidence, without unwanted sedative, respiratory or cardiovascular side effects.

Different pre- and peroperative factors may contribute to PONV and, if not correctly taken into account, introduce bias in the interpretation of results[1 16]. We found no difference in the preoperative state of patients or in their per- and postoperative courses. In particular, the amount of opioids used before and after operation did not differ between the two groups. As our patients represented a very homogeneous population, any difference in the occurrence of emetic symptoms may reasonably be attributed to the study drug.

We showed previously, in a controlled, randomized study, that thyroidectomy was a surgical procedure associated with a high incidence of PONV (up to 60%) when every mild symptom was taken as positive. This high incidence is probably related to the age range and sex of the patients (mostly middle-aged women) and intense peroperative vagal stimulation (surgical handling of the neck structures). In that study, prophylaxis with alizapride, a conventional antiemetic agent, reduced the incidence to only 40% compared with placebo[5]. In this study, 45% of patients (29 of 64) had PONV before the start of infusion of the study drug. Of the 13 (41%) symptomatic patients in the propofol group before infusion, only two were still vomiting during the first observation period. Only one patient was still slightly nauseous during the second observation period and then she became totally asymptomatic; however, she relapsed after the end of infusion. Otherwise, rapid and complete control of PONV was obtained with infusion of propofol at a rate of 1 mg kg^{-1} h^{-1}. In the control group, the overall incidence of PONV was 84% (51% before infusion and the remainder during infusion). This confirms the high incidence of PONV after thyroidectomy when no prophylaxis is used. In this group, PONV persisted throughout the infusion period, although there was a decrease in the frequency and severity of symptoms with time. As the two groups were comparable for all factors contributing to PONV, it may reasonably be concluded that the relief of symptoms was related to the antiemetic properties of propofol.

It is usually recommended that an antiemetic be given prophylactically before surgery or chemotherapy to improve the efficacy of the drug. As we wanted the effect of the drug to be dissociated completely from residual sedation caused by narcosis and no interference, the drug was given only when patients were sufficiently awake (sedation score of 1 or 2). Even with this less favourable regimen, complete response was obtained within less than 2 h in 94% of patients (30 of 32) and reached 100% success rate subsequently.

The mechanisms by which propofol acts as an antiemetic are unclear. The mechanisms of vomiting are complex and have been reviewed elsewhere[1]. Propofol is not thought to have vagolytic properties[12]. Borgeat and colleagues suggested that propofol may have failed as an antiemetic in patients who had undergone laparoscopic gynaecological procedures because of uninhibited vagal stimulation[12]. In our study, propofol was completely successful in the treatment of emetic symptoms after thyroidectomy, a procedure also accompanied by intense surgical stimulation of vagal afferents. However, the location and nature of this stimulation are not comparable with laparoscopy and do not involve irritation or distension of gastrointestinal structures that may convey chemoception or nociception via other afferents than parasympathetic. This suggests that the failure of propofol in the study of Borgeat and colleagues may not have been related wholly to absence of vagal inhibition. Other mechanisms for the non-hypnotic actions of action of propofol, including its antiemetic properties, have been reviewed recently[17 18]. A sedative effect of propofol, as sometimes suggested[17], can be ruled out in our patients as first, the degree of sedation was the same in both groups and second, sedation decreased with time in all patients whereas the efficacy of propofol increased. None of our patients had a sedation score higher than 2. Low doses of propofol may induce anxiolysis[19] sufficient to modify cortical afferents to the vomiting centre. Although we did not specifically test the anxiety status of our patients, clinical data describe no behavioural difference and indirectly indicate that an anxiolytic effect, if present, is not important enough to be the principal factor. A dopamine D2 receptor antagonist effect has also been suggested[20], but not proved. Propofol has also been shown to possess weak anti-serotonin ($5HT_3$) properties[21], suggesting a possible effect on the CTZ, but not enough to fully explain the efficacy of the drug in emetic syndromes refractory to $5\text{-}HT_3$ antagonist therapy[11]. The exact mechanisms by which propofol acts remain subject to speculation and await further studies.

The exact concentration at which propofol exerts its antiemetic properties is not well documented[22]. A blood concentration of 197 ng ml^{-1} has been reported in one patient after 48 h of propofol infused at a rate of 1 mg kg^{-1} h^{-1} for the treatment of refractory PONV[13]. An i.v. bolus of 10 mg (sometimes repeated once) is usually effective for approximately 30 min in the treatment of chemotherapy-induced emesis[12]. From the pharmacokinetic models available, it is suggested that the effective concentration range is very low, certainly less than 0.5 µg ml^{-1}[23]. These values are lower than those recommended for sedation[24]. As already mentioned, in this study, the efficacy of propofol increased while sedation decreased with time. This provides another argument against an association between the sedative and antiemetic properties of propofol.

Can infusions of propofol of prolonged duration interact with lipid metabolism because of the emulsion (10% Intralipid) formulation of the drug? After several days of sedation with propofol in intensive care units, at a dose range of 1–3 mg kg^{-1} h^{-1}, no subsequent modifications in triglycerides or fatty accumulation were reported[25]. Hence, no changes would be expected in our patients, as propofol was infused at lower doses for a shorter period of time.

The lowest rate necessary to achieve an antiemetic effect and the corresponding plasma concentration of propofol need to be defined more precisely if propofol is to be considered an acceptable regimen for the prevention and treatment of PONV in patients at risk of such symptoms. We did not study the financial impact (benefits *vs* costs) of this therapy and this should be done, including not only the cost of the drug and the material used but all other relevant factors[11 26 27]: efficacy, psychological satisfaction, decreased strain on the nursing staff, postoperative surgical course (haematoma, healing) and duration of hospital stay. At present, considering the efficacy and high degree of acceptance and satisfaction of the treatment, we believe that propofol may be proposed prophylactically as an antiemetic agent in patients identified at high risk of PONV or as rescue drug in case of failure of conventional antiemetic therapy. It should be noted that 5-HT$_3$ antagonists have also been used successfully in this situation, although the success rate did not reach 100%[28]. To our knowledge, no controlled study has directly compared the respective efficacy and costs of propofol and 5-HT$_3$ antagonists.

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References

1. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment and prevention. *Anesthesiology* 1992; **77**: 162–184.
2. Kenny GNC. Risks factors for postoperative nausea and vomiting. *Anaesthesia* 1994; **49** (Suppl.): 6–10.
3. Dejonckheere M, Deloof T, Dustin N, Ewalenko, P. Alizapride in the prevention of post-thyroidectomy emetic sequelae. *European Journal of Anaesthesia* 1990; **7**: 421–427.
4. Kortilla K, Oestman P, Faure E, Apfelbaum JL, Ekdawi M, Roizen MF. Randomized comparison of outcome after propofol–nitrous oxide and enflurane–nitrous oxide anaesthesia in operations of long duration. *Canadian Journal of Anaesthesia* 1989; **36**: 651–657.
5. Kortilla K, Oestman P, Faure E, Apfelbaum JL, Prunskis J, Ekdawi M, Roizen MF. Randomized comparison of recovery after propofol–nitrous oxide versus thiopentone–isoflurane–nitrous oxide anaesthesia in patients undergoing ambulatory surgery. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 400–403.
6. Martin TM, Nicolson SC, Bargas MS. Propofol anesthesia reduces emesis and airway obstruction in pediatric outpatients. *Anesthesia and Analgesia* 1993; **76**: 144–148.
7. Raftery S, Sherry E. Total intravenous anaesthesia with propofol and alfentanil protects against postoperative nausea and vomiting. *Canadian Journal of Anaesthesia* 1992; **39**: 37–40.
8. Reimer EJ, Montgomery CJ, Bevan JC, Merrick PM, Blackstock D, Popovic V. Propofol anaesthesia reduces early postoperative emesis after paediatric strabismus surgery. *Canadian Journal of Anaesthesia* 1993; **40**: 927–933.
9. Valanne J. Recovery and discharge of patients after long propofol infusion vs isoflurane anaesthesia for ambulatory surgery. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 530–533.
10. Borgeat A,Wilder-Smith OHG, Wilder-Smith CH, Forni M, Suter PM. Propofol improves patient comfort during cisplatin chemotherapy. A pilot study. *Oncology* 1993; **50**: 456–459.
11. Scher CS, Amar D, McDowall R, Barrst S. Use of propofol for the prevention of chemotherapy induced nausea and emesis in oncology patients. *Canadian Journal of Anaesthesia* 1992; **39**: 170–172.
12. Borgeat A, Wilder-Smith OHG, Saiah M, Kaplan R. Subhypnotic doses of propofol possess antiemetic properties. *Anesthesia and Analgesia* 1992; **74**: 539–541.
13. Schulman SR, Rockett CB, Canada AT, Glass PSA. Long term propofol infusion for refractory postoperative nausea: a case report with quantitative propofol analysis. *Anesthesia and Analgesia* 1995; **80**: 636–637.
14. Oestman L, Faure E, Glosten B, Kemen M, Robert MK, Bedwell S. Is the antiemetic effect of the emulsion formulation of propofol due to the lipid emulsion? *Anesthesia and Analgesia* 1990; **71**: 536–540.
15. Bellville JW, Bross IDJ, Howland WS. A method for the clinical evaluation of antiemetic agents. *Anesthesiology* 1959; **20**: 753–760.
16. Larsson S, Lundberg D. A propective study of postoperative nausea and vomiting with special regard to incidence and relations to patients characteristics, anaesthetic routines and surgical procedures. *Acta Anaesthesiologica Scandinavica* 1995; **4**: 539–545.
17. Borgeat A, Wilder-Smith OHG, Suter P. The non hypnotic therapeutic applications of propofol. *Anesthesiology* 1994; **80**: 642–656.
18. Smith I, White PF, Nathanson M, Gouldson R. Propofol: an update on its clinical use. *Anesthesiology* 1994; **81**: 1005–1043.
19. Cavazzuti M, Porro CA, Barbieri A, Galetti A. Brain and spinal cord metabolic activity during propofol anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 490–495.
20. DiFlorio T. Is propofol a dopamine antagonist? *Anesthesia and Analg*esia 1993; **77**: 200.
21. Barann M, Göthert M, Fink K, Bönisch H. Inhibition by anaesthetics of ^{14}C guanidinium flux through the voltage-gated sodium channel and the cation channel of the 5HT$_3$ receptor of N1E^{-1}15 neuroblastoma cell. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1993; **347**: 125–132.
22. Schulman S, Canada A, Ginsberg A. Serum propofol level associated with antiemetic effect. *Anesthesia and Analgesia* 1995; **80** (Suppl. 2): S419.
23. Vuyk J, Engbergs FHM, Lemmens HJM. Pharmacodynamics of propofol in female patients. *Anesthesiology* 1992; **77**: 3–9.
24. Mackenzie N, Grant IS. Propofol for intravenous sedation. *Anaesthesia* 1987; **42**: 3–6.
25. Gottardis M, Khünl-Brady KS, Koller W, Sigl G, Hackl JM. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. *British Journal of Anaesthesia* 1989; **62**: 393–396.
26. Cade L, Morley PT, Ross AW. Is propofol cost-effective for day-surgery patients? *Anaesthesia and Intensive Care* 1991; **19**: 201–204.
27. Green G, Jonsson L. Nausea: the most important factor determining the length of stay after ambulatory anaesthesia. A comparative study of isoflurane and/or propofol techniques. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 742–746.
28. Russel D, Kenny GNC. 5-HT3 antagonists in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; (Suppl.1): 63S–68S.

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Use of a mechanical simulator for training in applying cricoid pressure

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Summary

Using an airway management training model, we have assessed anaesthesia personnel in their use of correct cricoid force and ability to retain this skill after a short training programme. A perspex device, working on a hydraulic principle, was used to measure cricoid pressure when applied to the model. After initial assessment at two levels of cricoid force (20 and 40 N), participants undertook additional training on 3 consecutive days. Thereafter, available participants underwent reassessment at 14–21 days. Forty-nine anaesthetic assistants and anaesthetists underwent initial assessment and 18 completed the full training and reassessment. Untrained, the majority (63%) of participants applied inadequate cricoid force with a wide variation (mean 16.8 (SD 9.3) (range 4.5–43.0) at 20 N and 32.9 (13.3) (14.9–74) at 40 N). After a single training session there was a marked improvement in application of cricoid force. Two additional training sessions did not provide further improvement. After 14–21 days the ability of participants to apply correct cricoid force was retained by 72% of subjects. Those who applied inadequate cricoid force initially were more likely to do so even after training. Most subjects applied too great a cricoid force in the first 5 s of application followed by a progressive loss of force during the next 20 s. This trend improved after training. We conclude that the majority of untrained personnel apply inadequate cricoid force, placing patients at risk of aspiration of gastric contents. While a simple training programme improved application of cricoid force, retained for up to 3 weeks, there was often a substantial decrease in the force applied to the cricoid during a single application, even after training. (*Br. J. Anaesth.* 1996;**77**:468–472)

Key words

Larynx, cricoid pressure. Anaesthetist, training. Model, simulation. Complications, regurgitation. Intubation tracheal, training.

Use of cricoid pressure, as described by Sellick in 1961[1], is the cornerstone of rapid sequence induction to minimize the risk of pulmonary aspiration of gastric contents. The force required to occlude the oesophagus has been described "as moderate then firm pressure" [1] or "pressure which would cause pain when applied to the bridge of the nose" [2]. Quantitatively, Wraight, Chamney and Howells showed that a force of 44 newtons (N) should protect 50% of patients from regurgitation[3] while Vanner and colleagues[4] showed that 40 N would increase upper oesophageal sphincter pressure (UOSP) above awake levels in 100% of subjects. However, for the awake patient 40 N is poorly tolerated[5] and may cause coughing or vomiting[3]. In addition, Vanner and colleagues showed that UOSP decreased during induction of anaesthesia with thiopentone and suggested that 20 N be applied to the awake patient increasing to 40 N on loss of consciousness[6]. In clinical practice, Howells and colleagues[7] demonstrated that the force applied by anaesthesia assistants varies widely, resulting in a proportion of patients remaining at risk of regurgitation because of inadequate pressure. Devices have been described[3 4 7] which allow the exact force to be applied but manual application remains the commonest method.

To reduce the proportion of patients at risk of inhalation during induction, the person applying cricoid pressure should do so correctly. This study was designed to assess, using a model, the performance of anaesthesia staff and assistants in applying cricoid pressure. Participants then underwent a training programme using the model, which was subsequently used to evaluate retention of training.

Subjects and methods

To measure the force applied to the cricoid cartilage, we designed a device which was easy to use and calibrate, and was accurate over the intended range of forces (5–60 N). The perspex device worked on the hydraulic principle (fig. 1) and allowed cricoid pressure to be applied using a three-finger technique onto the cricoid cartilage of a model (Laerdel airway management trainer, fig. 2). The device was light (50 g) and applied a minimal force (0.49 N) when placed alone on the cricoid. The yoke transmitted the force from the cricoid to the plunger which abutted the diaphragm, increasing the fluid pressure within the device in a linear fashion (r=0.98). Pressure changes were transduced electronically and displayed as a moving line on an oscilloscope (Datascope 2000 pressure transducer). The absolute pressure (in mm Hg) was displayed also and recorded. For all measurements the level of the cricoid on the model

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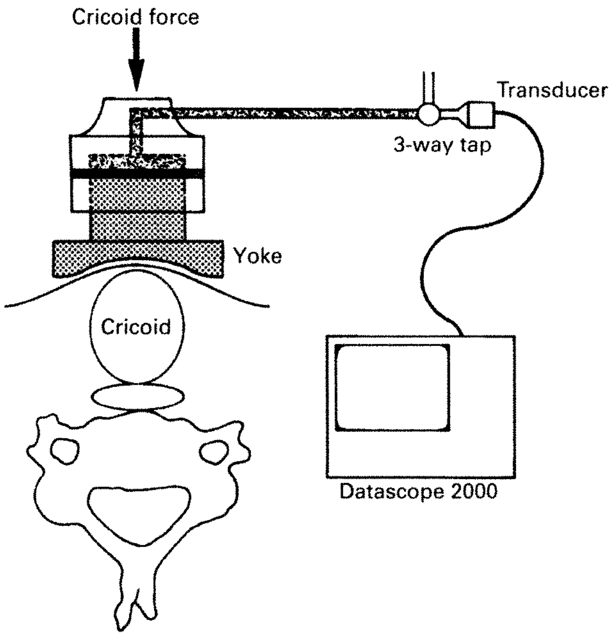

Figure 1 Cricoid force was applied to the yoke via the perspex device. The pressure developed was transduced and displayed as a moving line on an oscilloscope.

was 95 cm above ground and the transducer was zeroed at this level before each attempt. The device was calibrated using a set of electronic scales before each assessment (1 kg=9.81 N) (manufacturer's specifications available on request).

Both anaesthetists and anaesthesia assistants (nursing staff) were studied. The former are expected to be able to teach the correct force to be applied while the latter regularly apply cricoid pressure as part of their nursing duties. The end-point of the study was the ability of participants, without reference to the recording device (i.e. blinded), to apply two forces, 20 N and 40 N, within the range 2.5–5 N, respectively. Each subject was assessed before training, over the 3 days of training (consecutively if possible), and 14–21 days after the third day of training.

On day 1 the initial untrained assessment was made by blinding the subject to the pressure reading on the oscilloscope and asking the subject to apply, for a period of 20 s, what they considered their "normal" cricoid force. Each was then asked to apply "half their normal" force for 20 s. These two measurements were repeated three times. The mean force of three readings obtained over the last 15 s of application was recorded. After this initial assessment, each participant then viewed the oscilloscope screen unblinded and was allowed three attempts at attaining both 20 and 40 N. Participants were again blinded to the oscilloscope screen and asked to apply "half" and then "full" cricoid pressure three times. The forces developed were again recorded. If two of the three recorded forces and the mean force were appropriate (20±2.5 N and 40±5 N) the participant was considered trained for that day. If the targets were not met then additional cycles of unblinded training were followed by blinded reassessment until the participant was trained. The number of training cycles each day was recorded.

On days 2 and 3 the subjects first performed a blinded assessment at 20 and 40 N to assess retention from the previous day. If training targets were not met further training cycles were conducted as above. Two to 3 weeks later (according to staff availability) subjects were reassessed to determine retention of training. All assessments were performed by the same assessor (N. A.).

The numbers of subjects applying cricoid pressure correctly were compared on each day of training with the initial assessment using McNemar's chi-square test, with Bonferroni's correction for repeated measures. Mean force applied at each target value was compared with the target value using z tests, and repeated measures analysis of variance was used to compare mean values on each assessment with initial performance.

Results

Forty-nine staff participated in the initial assessment: 29 were anaesthetic assistants (all female) and 20 were anaesthetists (eight female) of varying years of experience. Eighteen of the subjects (six anaesthetic assistants, 12 anaesthetists) were available to complete the full training and reassessment.

Neither sex nor rank (i.e. assistants *vs* anaesthetists) significantly influenced the ability to apply the correct force during any part of the study. While not quantitatively assessed, we observed that most subjects applied a much greater force at the beginning of application than at the end of the 20s period and there was often an "overshoot" of applied force in the initial 5 s. This decline in applied force with time was still present after training but was less marked. Figure 3 shows examples of forces applied.

At the initial assessment, mean applied cricoid forces of 16.8 (SD 9.3) (range 4.5–43.0) N and 32.9 (13.3) (14.9–74) N were significantly ($P<0.01$ and <0.001, respectively) below the targets of 20 N and 40 N, respectively. The majority of subjects (67% at 20 N and 61% at 40 N) were unable to achieve the lowest force considered acceptable (17.5 N and 35 N, respectively). Only five subjects (10%) at 20 N and nine subjects (18%) at 40 N were able to apply pressures within the correct ranges.

Figure 4 shows the applied cricoid force at the targets of 20 and 40 N at the initial assessment and subsequent assessments after training for the 18 subjects who completed the training in full. At the initial assessment the only difference between the results of the 18 subjects who completed the study and the total of 49 subjects was that the difference between the mean force applied and 20 N was not statistically significant. Following training after the initial assessment on day 1 and subsequent training on days 2 and 3, there was a significant increase in the mean cricoid force applied at both the 20 and 40 N targets compared with the initial assessment. At the 40 N target, the mean values after training were within an acceptable range of the target value (35–45 N). At the 20 N target, however, mean values were greater than the upper limit of the acceptable range (17.5–22.5 N). Mean values at the 40 N target were significantly different from 40 N at the initial assessment ($z=3.02$, $P<0.01$) and after training on day 1 ($z=3.01$, $P<0.01$) but not on days 2 ($z=2.16$, $0.05>P>0.01$) or 3 ($z=1.96$, $0.05>P>0.01$). At the 20 N target, mean values did not differ significantly from

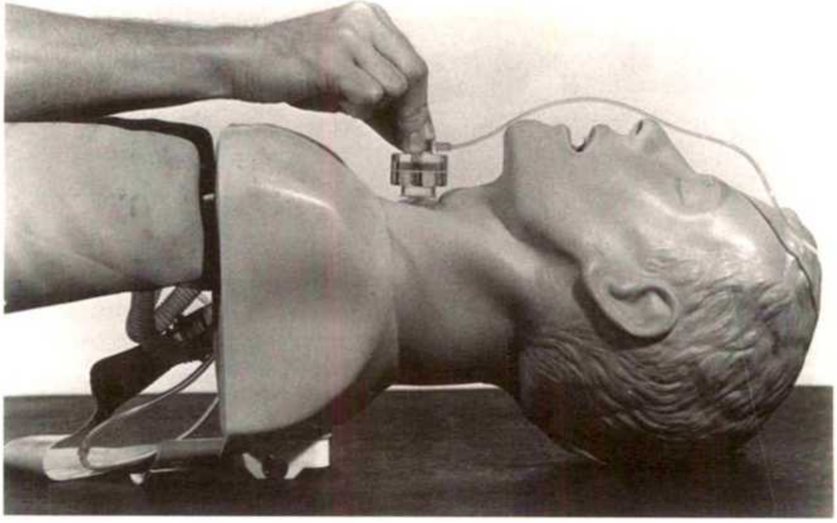

Figure 2 The cricoid measuring device was applied to an airway training model using a three-finger technique.

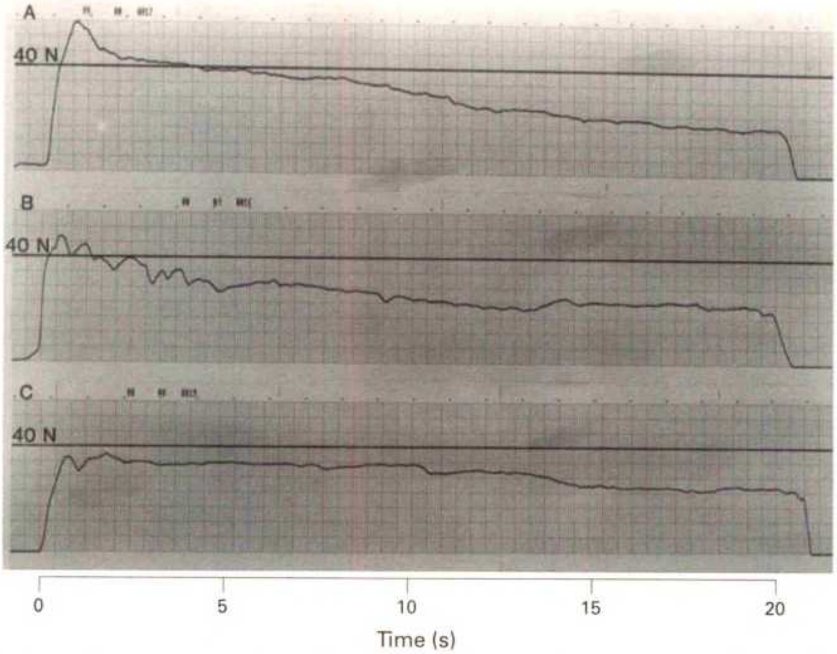

Figure 3 Three typical tracings of inadequate application of cricoid force. A and B show the marked initial overshoot and later decline of cricoid force while C shows the force to be low throughout, even though the subject had undergone training.

the target at the initial assessment (z=1.61, ns) or on day 1 (z=2.01, 0.05>P>0.01) but were significantly different on days 2 (z=3.11, P<0.01) and 3 (z=4.43, P<0.01).

There was a statistically significant (P<0.0125) reduction in the variability of applied pressures (coefficient of variation) at the 40 N target on days 1, 2 and 3 compared with the initial assessment. Coefficient of variations were 0.38 at the initial assessment, 0.13 on day 1, 0.17 on day 2 and 0.12 on day 3. At the 20 N target, however, a similar reduction in the coefficient of variation was seen only on days 1 and 3 (coefficient of variation for the 20 N target: initial 0.52; day 1, 0.27; day 2, 0.39; day 3, 0.25).

At the final assessment, 2–3 weeks after the last training cycle, the mean forces applied were within the acceptable range for both the 20 N and 40 N targets. At the 40 N target the mean force applied (38.9 (5.9) N) on the final assessment remained significantly higher than that obtained at the initial assessment (31.4 (12.0) N). Seven of the 18 subjects

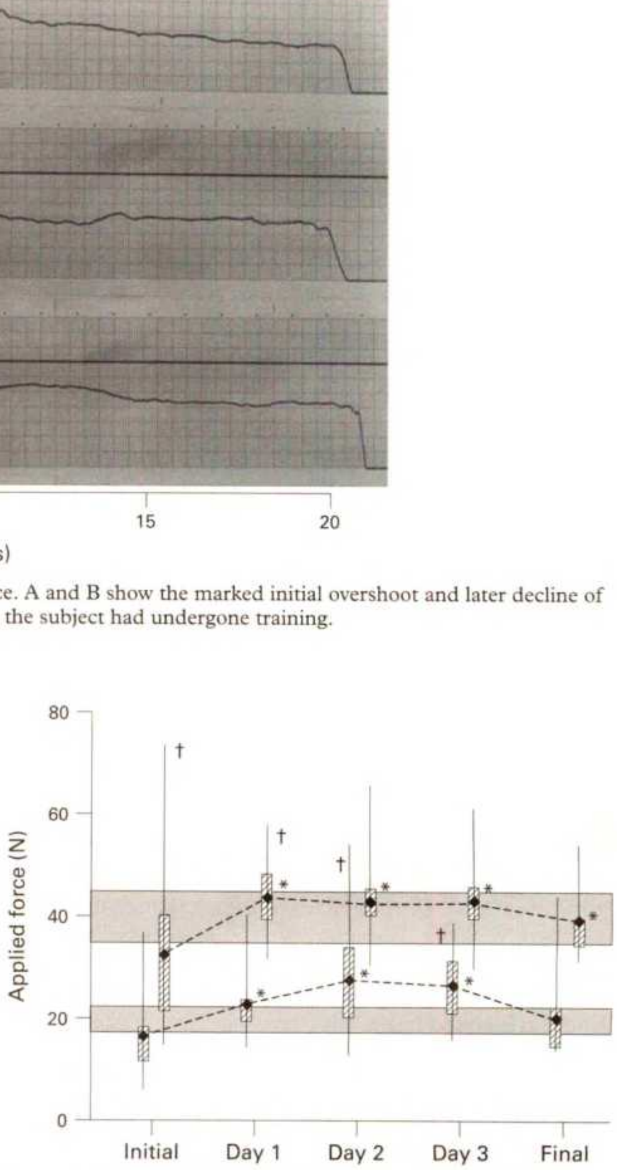

Figure 4 Cricoid force (mean, range and interquartile range) applied at the initial and subsequent assessments at the 20 N (bottom curve) and 40 N (top curve) targets. *P<0.05 compared with initial assessment; †P<0.05 compared with target value.

applied inappropriate cricoid force both at the initial and final assessments. At the final assessment two applied too much force, four applied 34 N and one 32 N. At the 20 N target there was no statistically significant difference between the mean force applied on the final day (20.3 (7.0) N) compared with the initial assessment (16.7 (8.7) N). However, at both 20 and 40 N targets the mean applied force was no longer significantly different from the target force (z=0.16 at 20 N, and 0.81 at 40 N, ns).

At the initial assessment only one subject at the 20 N target and three subjects at the 40 N target achieved cricoid forces within the acceptable range (table 1). Performance improved on subsequent days but a statistically significant (P<0.0125) improvement in the number of subjects achieving acceptable forces was only seen in the 40 N group on the final assessment. There was a trend towards an increase in the number of subjects applying too great a force during the training period but the sample was of insufficient size to obtain statistical significance.

One subject who applied a force within the acceptable range for the 20 N target at the initial assessment was outside the range at the final assessment. Between 1 and 3 training cycles were required after assessment on each day to achieve an applied force within the acceptable range at both the 20 N and 40 N targets. No statistically significant reduction in the number of training cycles required was observed during the training period.

Discussion

For cricoid pressure to prevent pulmonary aspiration of gastric contents, the UOSP generated must be greater than the pressure within the lower oesophagus. Wraight, Chamney and Howells[3] calculated that the maximum possible passive oesophageal pressure generated in a gravid patient given suxamethonium was 7.84 kPa, and showed further that this UOSP was generated in 50% of subjects given 44 N of cricoid force. Taking into account the force generated by a tracheal tube and accepting the resting awake UOSP of 38 mm Hg as an adequate target, Vanner and colleagues[4] showed that 100% of subjects with 40 N of cricoid force and 23 of 24 subjects with 35 N of cricoid force developed an adequate UOSP (>38 mm Hg). In a cadaver study, Vanner and Pryle[8] demonstrated that only 30 N was needed to develop an UOSP >35 mm Hg but how well cadavers at 4 °C correlate with anaesthetized patients is debatable. As all patients receiving a force greater than 35 N develop a sufficient UOSP to prevent aspiration, we used a target of 40±5 N as our upper target range for training. Our lower training target range of 20±2.5 N was used as a result of the study of Vanner and colleagues[6] who demonstrated that UOSP decreases before loss of consciousness thereby increasing the risk of regurgitation at this time, confirming earlier suggestions that cricoid force should be applied before loss of consciousness[1]. However, a full force of 40 N is tolerated poorly by awake patients[8] and may increase the risk of inducing airway obstruction[5], vomiting and even oesophageal rupture[8]. It seems prudent therefore to apply *moderate* (20 N) force before loss of consciousness, increasing to 40 N at the onset of anaesthesia.

Sixty one percent of the initial 49 participants failed to reach an adequate (> 35 N) force, 53% failing even to reach 30 N before training. This compares with the study of Howells and colleagues[7] where 47% of staff failed to reach 44 N and with the study of Vanner and colleagues[4] where 50% failed to increase UOSP above 35 mm Hg. The wide variation in applied force seen in our study compares well with the results of Howells and colleagues[7]. However, mean force was within acceptable limits in their study whereas in ours the mean force was below the target levels.

In the 18 subjects who completed training we saw a significant improvement in the applied force on day 1. The mean cricoid force was now within the correct range and the variability between subjects reduced. Only one subject now provided possibly dangerously low cricoid force (32 N). This confirms Sellick's suggestion that the application of cricoid force can be taught within a short period. However, 44% of subjects now applied forces in excess of 45 N which may damage the cricoid tissues or cause difficulty with intubation. It may be that some are untrainable and one advantage of the training programme would be to identify these staff.

The short training programme used in our study showed that after 14–21 days the ability to apply correct cricoid force was retained by most subjects. However, 28% of subjects still applied a force less than 35 N. As none of these subjects applied grossly inadequate force (<30 N) we consider this to be acceptable. This study was not designed to answer the question of how often training should be repeated, but work by Berden and colleagues[9] suggests that resuscitation skills in nurses are maintained for between 3 and 6 months and it would seem reasonable therefore that training should be repeated at least every 6 months. The evidence from this study is that retention of training deteriorates more rapidly.

The decrease in the applied force over the period of 20 s seen in our study has been observed previously[5]. The results give rise to concern about the

Table 1 Number of subjects applying cricoid force within and outside the acceptable ranges at the 20 N and 40 N targets (n=18). * P < 0.0125; † 0.05 > P > 0.0125 compared with initial percentage of participants applying inadequate cricoid pressure

	Target 20±2.5 N			Target 40±5 N		
	< 17.5 N	17.5–22.5 N	> 22.5 N	< 35 N	35–45 N	> 45 N
Initial	13	1	4	12	3	3
Day 1	3	8†	7	1	9	8
Day 2	2	6	10	2	10†	6
Day 3	2	3	13	2	10	6
Day 14–21	6	8†	4	5	11*	2

quality of cricoid force applied over a protracted period during, for example, a difficult intubation.

The inadequate force applied, the wide individual variability seen particularly at 20 N, and the decline in applied force with time in untrained personnel strengthen the argument for the need for a mechanical device to allow correct cricoid force to be applied consistently. However, a questionnaire conducted by Howells and colleagues suggested that only 33% of anaesthetists in the UK and USA believed a mechanical device would be useful and only 46% believed a training device necessary[7]. Many devices[2-4 10] have been described and demonstrated to be effective in training subjects to apply correct cricoid force but none have been adopted into general practice possibly because they have been associated with laryngeal distortion and difficult intubation[10]. Our device being smaller and lighter may allow more accurate placement, reducing laryngeal distortion, although this has yet to be assessed.

We conclude that training improves performance but retention of the skill of applying appropriate cricoid pressure for any length of time cannot be guaranteed. Indeed some staff may be untrainable. Our results imply that staff applying cricoid pressure should undergo a frequent training programme, the interval of which remains to be determined but may need to be monthly. Introducing such training programmes into clinical practice may well be logistically prohibitive. Alternatively such programmes may form part of courses in airway management. In addition, the value of introduction of such training programmes in the context of improved morbidity or mortality from such a rare event as acid aspiration is unlikely to be significant. Nevertheless if cricoid pressure is to be applied then only appropriate techniques can be acceptable. While the idea of applying moderate cricoid pressure (20 N) before induction is laudable, the difficulty experienced by our subjects in attaining this pressure suggest that this goal may be difficult to achieve.

Acknowledgements

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References

1. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961; **2**: 404–406.
2. Lawes EG. Cricoid pressure with or without the "cricoid yoke". *British Journal of Anaesthesia* 1986; **58**: 1376–1379.
3. Wraight WJ, Chamney AR, Howells TH. The determination of an effective cricoid pressure. *Anaesthesia* 1983; **38**: 461–466.
4. Vanner RG, O'Dwyer JP, Pryle BJ, Reynolds F. Upper oesophageal sphincter pressure and the effect of cricoid pressure. *Anaesthesia* 1992; 47: 95–100.
5. Vanner RG. Tolerance of cricoid pressure by conscious volunteers. *International Journal of Obstetric Anaesthesia* 1992; **1**: 195–198.
6. Vanner RG, Pryle BJ, O'Dwyer JP, Reynolds F. Upper oesophageal sphincter pressure and the intravenous induction of anaesthesia. *Anaesthesia* 1992; 47: 371–375.
7. Howells TH, Chamney AR, Wraight WJ, Simons RS. The application of cricoid pressure. An assessment and survey of its practice. *Anaesthesia* 1983; 38: 457–460.
8. Vanner RG, Pryle BJ. Regurgitation and oesophageal rupture with cricoid pressure: a cadaver study. *Anaesthesia* 1992; **47**: 732–735.
9. Berden HJJM, Williems FF, Hendrick JMA, Pijls NHJ, Knape JTA. How frequently should basic cardiopulmonary resuscitation training be repeated to maintain adequate skills. *British Medical Journal* 1993; 306: 1576–1577.
10. Lawes EG, Duncan PW, Bland B, Gemmel L, Downing JW. The cricoid yoke—a device for providing consistent and reproducible cricoid pressure. *British Journal of Anaesthesia* 1986; 58: 925–931.

British Journal of Anaesthesia 1996;77:473–479

Endotoxaemia and postoperative hypermetabolism in coronary artery bypass surgery: the role of ketanserin

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Summary

In a randomized, double-blind clinical study in 29 patients undergoing elective coronary artery surgery, we assessed the role of ketanserin, an inhibitor of serotonin-induced vasoconstriction and weak α_1 sympathetic blocker, in reducing endotoxaemia and postoperative hypermetabolism. Male patients without major organ dysfunction were allocated randomly to receive either ketanserin or placebo. Hypermetabolism was defined as an increase in oxygen consumption in the early postoperative hours ($\Delta\dot{V}o_2$). Circulating endotoxin (P=0.04) and postoperative $\Delta\dot{V}o_2$ (P=0.03) were lower in the ketanserin patients. Endotoxaemia was associated also with low vascular filling. From these preliminary results we conclude that treatment with ketanserin during cardiac surgery may reduce but not abolish endotoxaemia and postoperative hypermetabolism. (*Br. J. Anaesth.* 1996;**77**:473–479)

Key words

Surgery, cardiovascular. Complications, endotoxaemia. Oxygen, consumption. Metabolism, oxygen consumption. Pharmacology, ketanserin.

The postoperative course after cardiac surgery may be complicated by a systemic inflammatory response[1 2]. This hypermetabolic response is multifactorial. It may be caused by rewarming after hypothermia[3], complement activation on contact of blood with material from the extracorporeal circuit[4–6] or reperfusion after ischaemia. It has also been associated with endotoxaemia and subsequent cytokine release[7]. Circulating endotoxin during cardiac surgery possibly originates from the patient's own gut flora. Endotoxin permeating from the gut stimulates the host to produce inflammatory mediators that cause the systemic inflammatory response[7–9].

One of three factors appear to be necessary for permeation of endogenous bacterial endotoxin from the gut into the systemic circulation: first, bacterial overgrowth in the gut lumen, second, loss of gut barrier function, and third, decreased ability of the reticuloendothelial system to detoxify the permeated endotoxin. The first factor is probably not important during cardiac surgery, but the two other factors may be. Both might be caused by splanchnic hypoperfusion, as may occur during cardiac surgery[10–12]. In a previous study it was found that during cardiac surgery intestinal permeability between cells increased. The amount of circulating endotoxin was related to this increase[13]. Increased intestinal permeability was associated with pharmacologically induced vasoconstriction and hypovolaemia during operation.

In rats, ketanserin has a beneficial effect on the occurrence of ischaemic lesions in the gastric mucosa[14 15]. Ketanserin inhibits the action of serotonin on the vasoconstricting 5-HT$_2$ receptor and on platelet aggregation. It also inhibits the potentiating vasoconstrictive effects of serotonin on noradrenaline and angiotensin, and has a weak α_1 receptor inhibiting effect at higher concentrations[16]. As a result, ketanserin inhibits vasoconstriction and platelet aggregation. This effect is particularly prominent in vessels with decreased endothelial-mediated vasodilatation[17].

The first aim of this study was to assess if i.v. administration of ketanserin reduces the degree of endotoxaemia during elective coronary artery bypass surgery and ameliorates the postoperative hypermetabolic response. The second aim was to assess if, in addition to ketanserin, other factors, such as haemodynamic state and duration of CPB[13 18], are associated with endotoxaemia. Therefore, we have measured the concentration of circulating endotoxin, haemodynamic state and postoperative increase in oxygen consumption in patients receiving i.v. ketanserin or placebo before, during and after coronary bypass surgery.

Patients and methods

Male patients, aged 45–75 yr, undergoing elective coronary artery bypass grafting without valve re-

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placement, were eligible for inclusion in the investigation when the following criteria were met: left ventricular ejection fraction more than 40% or an end-diastolic pressure in the left ventricle less than 20 mm Hg, and normal organ function. Patients were excluded if they had unstable angina pectoris, major coagulopathy, history of inflammatory bowel disease or alcohol abuse, had used corticosteroids, antibiotics, ketanserin or aprotinin in the week before operation, had ingested acetylsalicylic acid within 4 days before surgery, or had a QT interval on the electrocardiogram of more than 500 ms (QT prolongation is reported with higher doses of ketanserin). Written informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Free University Hospital, Amsterdam.

As it is not known if ketanserin has any effect on endotoxaemia, we undertook a pilot study. Patients were allocated randomly to receive, in a double-blind design, either ketanserin or a similar volume of placebo. Randomization was performed by Janssen Pharmaceutica BV. In the ketanserin group, patients received ketanserin 0.1 mg kg^{-1} h^{-1} i.v. for 4 h, beginning after induction of anaesthesia and insertion of the pulmonary artery catheter preceding sternal incision. To limit the hypotensive effects of ketanserin, the dose was reduced to 0.05 mg kg^{-1} h^{-1} after 4 h. The infusion was stopped 18 h after operation.

Endotoxin was measured in blood at baseline (directly after admission to the operating room), during cardiopulmonary bypass (CPB) (10 min after the onset of CPB and on termination of CPB), and in the intensive care unit (ICU) (30 min, 2 h and 18 h after admission). In addition, a sample of the prime fluid of the heart–lung machine was obtained before connection to the patient (ET prime).

Clinical measurements were made at baseline (after induction of anaesthesia and insertion of the pulmonary artery catheter), 30 min after termination of CPB and in the ICU (at fixed times of endotoxin sampling and additionally at 4 and 8 h after admission to the ICU).

The amount of endotoxin appearing in the systemic circulation and the postoperative hypermetabolic response were the end-points of the study. We chose endotoxaemia as the primary end-point as we hypothesized that inhibition of vasoconstriction would improve intestinal and hepatic perfusion and reduce the subsequent permeation of endotoxin from the gut into the systemic circulation. The amount of circulating endotoxin concentration during operation and the concentration of endotoxin at the time of patient admission to the ICU (ET_{ICU}) were measurements of special interest. Postoperative hypermetabolism was chosen as the clinical endpoint as it was shown that postoperative hypermetabolism was associated with the endotoxin-related inflammatory response[7]. Because we studied patients at low risk of postoperative complications, we did not expect to find an effect on duration of ICU stay.

On the morning of surgery, patients received their usual cardiac medication and lorazepam. Anaesthesia was induced with fentanyl 30 μg kg^{-1} and pancuronium 0.1 mg kg^{-1}, and maintained with a continuous infusion of midazolam and additional doses of fentanyl up to 50 μg kg^{-1}. Volatile anaesthetics, nitrous oxide or corticosteroids were not given. The lungs were ventilated with 40% oxygen and a positive end-expiratory pressure of 5 cm H_2O. A pulmonary artery catheter was inserted after induction of anaesthesia and tracheal intubation.

CPB was performed with moderate systemic hypothermia (28–30 °C), non-pulsatile flow and cold crystalloid cardioplegia for myocardial protection. The CPB circuit consisted of a membrane oxygenator (Avecor, Plymouth, MN, USA), a roller pump (Stockert) with an arterial filter and polyvinyl tubing. The circuit was primed with Ringer's lactate 2000 ml, 20% human albumin 200 ml, 20% mannitol 100 ml, 8.4% sodium bicarbonate 50 ml and bovine heparin 5000 u. A standard cannulation technique was used with a two-stage venous cannula, an arterial cannula in the ascending aorta and subtotal bypass. During CPB, pH was regulated according to the α-stat concept. Rewarming was started just before the last distal anastomosis was made by slowly increasing temperature, at first to 32 °C and then to 39.5 °C. Rewarming was continued until nasopharyngeal temperature was >36.5 °C.

After releasing the aortic cross-clamp, nitroglycerine 2 mg h^{-1} and dopamine 2 μg kg^{-1} h^{-1} were started. Fluid therapy was titrated according to cardiac filling pressures and cardiac index. Target values were as follows: central venous pressure (CVP) 8–10 mm Hg, pulmonary artery occlusion pressure (PAOP) 12 mm Hg and cardiac index (CI) >2.5 litre min^{-1} m^{-2}. In the ICU all patients were warmed externally with a heating mattress until rectal temperature exceeded 36.5 °C and the difference between rectal and toe temperature was less than 5 °C. All patients received controlled mechanical ventilation for at least 8 h after operation. Doses of dopamine and nitroglycerin were increased when cardiac index remained low after adequate filling. Packed cells were transfused to maintain haemoglobin >8.8 g dl^{-1}. In order to relieve pain and stress, prevent shivering and obtain a reliable value of oxygen consumption and cardiac output, patients were sedated with morphine 5–10 mg i.v. and diazepam 5–10 mg i.v. for 8 h after operation. After that, when temperature and circulation were stable, patients were allowed to wake up, pressure support ventilation was started and the trachea was extubated generally in the morning after operation.

Blood for measurement of endotoxin was obtained from a newly inserted radial artery catheter or from the arterial cannula of the extracorporeal circuit. Blood samples were collected in tubes (Monovette, Sarstedt, Nümbrecht, Germany) containing pyrogen-free heparin (Thromboliquine, Organon, Oss, The Netherlands) at a final concentration of 30 u. ml^{-1}, under endotoxin-free conditions, and were immersed immediately in ice. Platelet-rich plasma was prepared directly by centrifugation (4 °C) at 190 *g* for 10 min and stored immediately at −70 °C. Endotoxin was measured with an optimized chromogenic assay (Coatest Endotoxin, Kabi-Chromogenix, Mölndal, Sweden) based on the lipopolysaccharide-dependent activation of Limulus amoebocyte lysate (LAL) and subsequent measurement of the activated LAL enzyme(s) with a chromogenic substrate. This assay has been described previously[19]. The LAL material contained in this batch of Coatest endotoxin kits is insensitive to LAL-reactive material such as β-glucan[20]. The assay has a detection limit of 0.036 EU ml^{-1} (endotoxin units per millilitre of platelet rich plasma). This corresponds to 3 pg ml^{-1} of the endotoxin standard used in this study.

Haemodynamic measurements included heart rate, arterial pressure, CVP, pulmonary artery pressure, PAOP and cardiac output using an arterial and pulmonary artery catheter. Cardiac output was measured by the thermodilution method using room temperature injectate. The mean of four measurements was calculated. Cardiac index (CI) was calculated from cardiac output: CI=cardiac output/total body area.

Oxygen consumption ($\dot{V}O_2$) was measured continuously by respiratory gas analysis with an open circuit indirect calorimeter (Deltatrac, Datex Instrumentarium, Helsinki, Finland) as long as the patient was undergoing artificial ventilation. This metabolic monitor has been validated previously[21] and described in detail[22]. FI_{O_2} was always less than 50%. Minute volume and FI_{O_2} remained constant for 60 min before measurements were obtained. Calibrations were made before starting, after transport of the patient and instrument to the ICU and at 8-h intervals thereafter. A meticulous check on gas leakage was made; minute volume, as measured by the ventilator and the calorimeter, was checked routinely. Care was taken that the patient was sedated adequately and shivering was prevented. The Deltatrac calorimeter averages $\dot{V}O_2$ measurements over a period of 1 min, and the mean of at least five measurements was taken. These values were also compared with the continuously printed values to exclude short-term variability. Values of $\dot{V}O_2$ were adjusted for total body area (ml min^{-1} m^{-2}).

Hypermetabolic response was assessed by the postoperative increase in oxygen consumption from baseline ($\Delta\dot{V}O_2$)[7]. Oxygen supply was calculated according to the following equation: oxygen supply = CI × (1.39 × haemoglobin (g dl^{-1}) × arterial oxygen saturation+0.0031 × Pa_{O_2}

DATA ANALYSIS

Statistical analysis was performed using Statview SE+ Graphics computer software (Abacus concepts, Berkeley, CA, USA). Data are presented as mean (SEM). Individual measurements were compared between groups using a two-tailed Student's *t* test for unpaired observations and serial measurements between groups with a two-way analysis of variance (ANOVA) with a design for repeated measures. For single measurements of special interest in a series, Bonferroni's correction for repeated measurements was made. To quantify the amount of endotoxin in the systemic circulation during operation between groups, the area under the curve (AUC) was calculated for the concentration–time curve[23]. To correct for differences in the duration of CPB, AUC was divided by total time[23].

In the analysis of $\Delta\dot{V}O_2$, measurement of $\Delta\dot{V}O_2$ 2 h after admission to the ICU was of special interest, as this value was related to the inflammatory response to endotoxaemia[7]. The time pattern of $\Delta\dot{V}O_2$ in the ketanserin group was different from that in the placebo group, making a two-way ANOVA for repeated measures inappropriate. We therefore compared mean postoperative $\Delta\dot{V}O_2$ (AUC from 30 min to 8 h after ICU admission) between groups.

Regression analysis was performed in the entire group of patients (ketanserin and placebo) to investigate if variables, other than ketanserin, could explain the remaining variability of ET_{ICU} and $\Delta\dot{V}O_2$. A two-sided *P* value of less than 0.05 was considered statistically significant.

Results

We studied a total of 31 consecutive male patients undergoing CPB for elective coronary artery bypass grafting. Study medication was stopped prematurely in two patients (one in each group) because of severe bleeding and myocardial ischaemia before the onset of CPB. These patients were excluded from the study before unblinding and analysis. In total, 14 patients were treated with ketanserin and 15 patients received placebo. In one placebo patient, the endotoxin results could not be measured for technical reasons. All other data were evaluated.

There were no significant differences in patient characteristics, preoperative myocardial function, surgical characteristics (table 1) or baseline haemodynamics (table 2). All patients were discharged from the ICU on the first day after operation and all survived. Re-operation for postoperative bleeding was necessary once in each treatment group. In the ketanserin group, two patients had peroperative myocardial infarction as a result of incomplete revascularization.

COMPARISON OF ENDOTOXIN CONCENTRATIONS

Circulating endotoxin, analysed using two-way analysis of variance for repeated measures with all measurements included, was lower in patients treated with ketanserin than in placebo patients (P=0.04). There was no significant group–time interaction (P>0.5) (fig. 1). In nine of 14 patients in the placebo group, and in two of 14 patients in the ketanserin group, endotoxin concentration was positive 10 min after the start of CPB compared with baseline (P<0.05). At the end of CPB, endotoxin concentration was positive in 12 of 14 patients in the placebo group and in eight of 14 in the ketanserin group (ns). The mean concentration of circulating endotoxin during operation (AUC/time) was 0.130

Table 1 Patient data (mean (SEM or range) or number))

	Placebo group	Ketanserin group
Preoperative		
Age (yr)	61.1 (49–74)	69.6 (47–73)
Left ventricular end-diastolic pressure (mm Hg)	9.9 (0.89)	11.8 (1.0)
Long-acting vasodilators (*n*)	15	13
Surgery		
Aortic cross-clamp time (min)	70 (5.5)	80 (6.6)
Cardiopulmonary bypass time (min)	110 (7)	119 (10)
No of distal anastomoses (median (range))	4 (2–6)	4 (1–7)

Table 2 Mean (SEM) haemodynamic measurements and oxygen delivery in the placebo (P) and ketanserin (K) groups. HR = heart rate, MAP = mean arterial pressure (mm Hg), CVP = central venous pressure (mm Hg), POAP = pulmonary artery occlusion pressure (mm Hg), CI = cardiac index (l litre^{-1} min^{-1} m^{-2}), Do_2I = oxygen delivery (ml min^{-1} m^{-2}), SVRI = systemic vascular resistance (dyn s cm^{-5} m^2). *Significant difference between groups (two-factor ANOVA for repeated measures)

	Baseline	30 min after CPB	30 min ICU	2 h ICU	4 h ICU	8 h ICU	18 h ICU
HR							
P	58 (2.9)	88 (5.2)	84 (5.5)	89 (5)	82 (3.6)	89 (3.6)	87 (3)
K	63 (3)	92 (4.5)	92 (6.5)	86 (4)	85 (3.3)	85 (3.3)	82 (3)
MAP*							
P	74 (3.0)	81 (3.8)	80 (3.3)	79 (4.1)	73 (2.5)	72 (1.6)	79 (2.4)
K	74 (3.0)	75 (2.6)	74 (3.3)	72 (2.1)	70 (2.0)	68 (2.1)	74 (1.7)
CVP							
P	9.5 (0.9)	9.7 (0.6)	8.1 (0.6)	7.7 (0.5)	8.0 (0.6)	8.0 (0.5)	6.0 (0.7)
K	9.8 (0.9)	12 (0.9)	7.0 (0.7)	13.3 (1.0)	8.6 (0.4)	8.2 (0.7)	8.5 (0.7)
PAOP							
P	9.7 (0.9)	10.1 (0.9)	8.5 (0.6)	8.4 (0.6)	8.7 (0.7)	9.2 (0.5)	8.3 (1.0)
K	9.8 (0.5)	11.5 (0.6)	8.9 (0.9)	10.3 (1.0)	8.8 (0.6)	10.3 (0.7)	10.6 (0.7)
CI							
P	2.1 (0.1)	3.2 (0.2)	3.7 (0.2)	3.7 (0.2)	3.9 (0.2)	3.9 (0.2)	3.7 (0.2)
K	2.3 (0.1)	3.8 (0.3)	4.2 (0.3)	4.0 (0.3)	3.9 (0.2)	4.0 (0.2)	3.8 (0.1)
Do_2I							
P	165 (8.5)	175 (10.8)	202 (9.3)	225 (12)	208 (10)		228 (11)
K	184 (9.1)	198 (16)	237 (17)	219 (16)	200 (13)		228 (6)
SVRI							
P	2606 (124)	1835 (132)	1625 (117)	1592 (123)	1394 (94)	1376 (89)	1588 (90)
K	2340 (130)	1478 (182)	1414 (172)	1369 (131)	1304 (94)	1218 (89)	1384 (47)

EU ml^{-1} in the ketanserin group and 0.193 EU ml^{-1} in the placebo group, indicating a 33% reduction in endotoxaemia during operation in patients treated with ketanserin (P=0.03). The concentration of circulating endotoxin on admission to the ICU was 0.199 EU ml^{-1} in the ketanserin group and 0.314 EU ml^{-1} in the placebo group (P<0.05).

The mean concentration of endotoxin in the prime fluid was 0.123 (0.039) EU ml^{-1} in the ketanserin group and 0.078 (0.032) EU ml^{-1} in the placebo group (ns).

COMPARISON OF OXYGEN CONSUMPTION AND OTHER CLINICAL VARIABLES

$\Delta\dot{V}o_2$ 2 h after admission to the ICU was significantly lower in patients treated with ketanserin than in placebo patients (P<0.001). Postoperative $\Delta\dot{V}o_2$ (AUC) was 44% lower in the ketanserin group than in the placebo group (P=0.03) (fig. 2).

Mean arterial pressure was lower in the ketanserin than in the placebo group (P=0.04 with two-way ANOVA for repeated measures); the group–time interaction was not significant (P>0.5) (table 2). There was no significant difference in the other haemodynamic variables; oxygen supply (table 2), use of dopamine and postoperative concentrations of lactate. Blood loss and the use of blood products were not significantly different between groups. Fluid balance during surgery was not different between groups, but there was a trend towards a more positive fluid balance in the ICU in the ketanserin group. This difference started 4 h after admission to the ICU and coincided with increased administration of fluids to patients treated with ketanserin in the period from 4 to 18 h after ICU admission (P=0.03). Times for tracheal extubation and discharge from the ICU were not significantly different between groups (table 3).

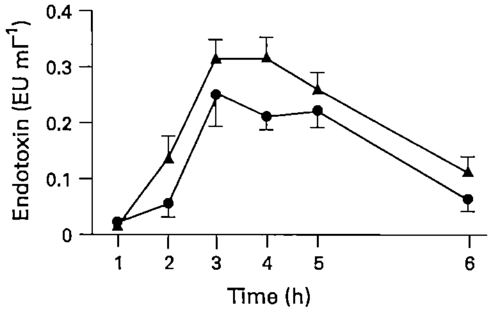

Figure 1 Plasma concentrations of endotoxin (mean, SEM) *vs* time for patients who received ketanserin (●) or placebo (▲) at the following times: baseline (after induction of anaesthesia and insertion of the pulmonary artery catheter) (1); 10 min after the start of CPB (2) and after termination of CPB (3); and in the ICU (30 min (4), 2 h (5) and 18 h (6) after admission). Circulating endotoxin (ANOVA) was significantly lower in ketanserin patients (P=0.04).

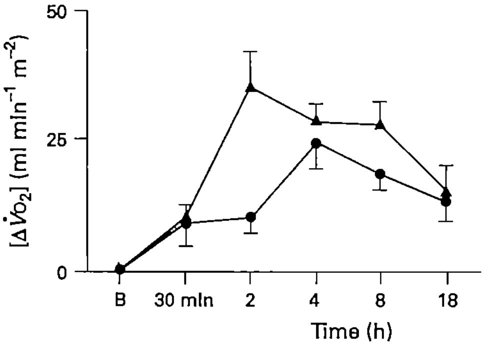

Figure 2 Increase in oxygen consumption ($\Delta\dot{V}o_2$) from baseline (B) (mean, SEM) for the ketanserin (●) and placebo (▲) groups 30 min and 2, 4, 8 and 18 h after admission to the ICU. Postoperative $\Delta\dot{V}o_2$ (AUC) was significantly lower in ketanserin patients (P=0.03).

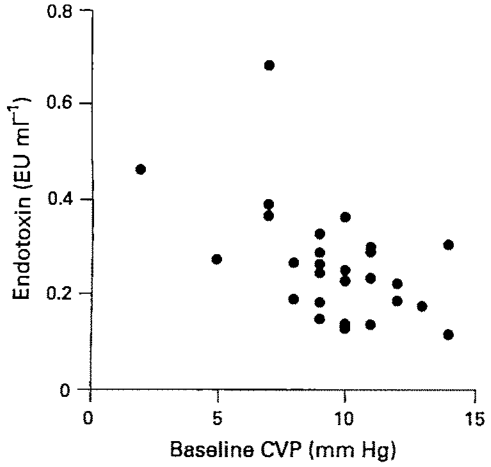

Figure 3 Relation between baseline central venous pressue (CVP) and the concentration of endotoxin on admission to the ICU (n=28, r=0.55, P=0.0036).

RELATION OF CIRCULATING ENDOTOXIN WITH OTHER VARIABLES

To investigate if haemodynamic variables could explain the variability of ET_{ICU}, these variables were used in a simple regression analysis, and then the significant factors were entered in a forward stepwise regression analysis. Baseline CVP, baseline PAOP and fluid balance during operation were significantly associated with ET_{ICU} (P<0.05). Of these, the relation between baseline CVP and ET_{ICU} was the most significant (fig. 3).

In the forward stepwise regression analysis, baseline CVP was entered first, fluid balance during operation and ketanserin treatment were entered next, and baseline PAOP was entered in the fourth step. After entering PAOP, CVP was removed from the model yielding a better fit after the other variables were entered. CVP and PAOP were interrelated. The final model is presented in table 4. ET_{ICU} was higher in patients with low baseline filling pressures, with a less positive fluid balance during operation in the placebo group. ET_{ICU} was not related to baseline CI or to duration of CPB. Endotoxin concentration 10 min after the start of CPB was not related to ET prime.

RELATION OF $\Delta\dot{V}O_2$ WITH OTHER VARIABLES

Apart from ketanserin, $\Delta\dot{V}O_2$ was related to ET_{ICU}. $\Delta\dot{V}O_2$ was not related to systemic oxygen supply, systemic vascular resistance, use of dopamine or concurrent temperature.

Table 3 Other clinical measurements (mean (SEM)). *Significant difference between groups. Extubation time and transfer from ICU were calculated from the patient's admission to the ICU

	Placebo group	Ketanserin group
Total blood loss (ml)	2160 (269)	2060 (269)
Fluid balance (operation) (ml)	3400 (243)	3777 (301)
Fluid balance (0–4 h ICU) (ml)	459 (248)	476 (302)
Fluid balance (4–18 h ICU) (ml)	1106 (387)	2176 (439)
Fluids (0–4 h ICU) (ml)	2991 (315)	3021 (251)
Fluids (4–18 h ICU) (ml)*	4608 (380)	6410 (714)
Extubation time (h)	20.4 (1)	22.8 (0.5)
Transfer from ICU (h)	24.8 (1.5)	25.9 (0.5)

Table 4 Determinants of the concentration of circulating endotoxin on the patient's admission to the ICU. The concentration of circulating endotoxin on ICU asmission (ET_{ICU} (EU ml^{-1}) can be expressed as a function of ketanserin treatment (1 = yes, 2 = no), fluid balance during operation (ml) and pulmonary artery occlusion pressure at baseline (mm Hg) in the following equation: $ET_{ICU} = 0.8-01$ (ketanserin treatment) $-(PAWP_{baseline})-0.067$ (fluid $balance_{operation}$). The F value describes the strength of the relation. $F \geq 4$ is considered statistically significant

Independent variable	Coefficient	SEM	F
Constant	0.8		
Ketanserin treatment (1/0)	−0.1	0.031	5.7
$PAOP_{baseline}$ (mm Hg)	−0.027	0.0061	19.6
Fluid $balance_{operation}$ (ml)	−0.067	0.016	16.4
r = 0.78, r^2 (adj) 0.57, F test of the model 12.7, P < 0.01			

Discussion

We have found that i.v. administration of ketanserin may reduce the degree of endotoxaemia during low-risk coronary bypass surgery, but does not prevent it. Ketanserin appeared to be more protective early after the onset of CPB than at the end. After the onset of CPB, tissue perfusion may decrease as a result of acute changes in vascular volume caused by haemodilution with a decrease in oncotic pressure[24], induction of hypothermia, extracorporeal circulation with non-pulsatile flow, and release of vasoactive substances such as angiotensin and noradrenaline[25 26]. Splanchnic vasoconstriction is one of the physiological compensation mechanisms maintaining blood flow to the heart and brain during such acute changes. However, subsequent splanchnic hypoperfusion may result in a loss of gut barrier function for intraluminal endotoxin and a decreased ability of the reticuloendothelial system to detoxify the permeated endotoxin.

The most plausible mechanism by which ketanserin reduces endotoxaemia is thought to be related to inhibition of vasoconstriction. This may lead to improvement in the microcirculation[17] and cardiac performance. However, this conclusion cannot be deduced directly from this study, as the splanchnic microcirculation was not measured. Nevertheless, our data give some indication. Patients with low baseline filling pressures and a less positive fluid balance during surgery had higher circulating endotoxin concentrations. The splanchnic vasoconstrictive response is thought to be more pronounced in patients with low vascular filling. While baseline filling pressures and fluid balance during operation were not significantly different between groups, ketanserin may have mitigated this response. That baseline filling pressures are important for ET_{ICU} and not baseline CI might be explained as follows. The major increase in circulating endotoxin occurred during CPB when the patient's heart is excluded from the circulation, and the heart–lung machine provides circulation, with pump flow standardized according to body surface area. Therefore, vascular filling and pump flow are the important determinants of circulation during CPB, and CI is irrelevant. After CPB, there was a trend towards a higher CI in the ketanserin group. This higher CI might also have contributed to a lower ET_{ICU} in patients treated with ketanserin, but may also have been an effect. Although our study design was not appropriate to explain the mechanism by which ketanserin reduced endotoxaemia, a combined strategy to reduce endotoxaemia may be advised. This strategy should aim at inhibition of vasoconstriction by the use of ketanserin and expansion of intravascular volume before, during and after CPB in the period that the patient is at risk for splanchnic vasoconstriction.

At the end of CPB, ketanserin appeared to be less effective. This might be attributed to the fact that maintenance of normovolaemia was not a goal of treatment during cardiopulmonary bypass. In addition, the use of the large prime fluid causing hypo-oncotic haemodilution may also have contributed to endotoxaemia[27]. At the end of CPB, other factors may also affect permeation of endotoxin into the systemic circulation, such as reperfusion of the ischaemic myocardium inducing distant tissue damage by circulating toxic mediators[28]. These might impair gut barrier function or detoxification of the permeated endotoxin by the RES, or both.

From the results of this study it also appears that treatment with i.v. ketanserin during low-risk coronary bypass surgery reduces $\Delta\dot{V}O_2$. In our study there was no evidence for a supply-limited $\dot{V}O_2$ in patients treated with ketanserin, as oxygen supply and lactate concentrations were not significantly different between groups. However, both ketanserin treatment and ET_{ICU} were associated with $\Delta\dot{V}O_2$. The effect of ketanserin on $\Delta\dot{V}O_2$ was probably related to its effect on endotoxaemia, but might also be the result of better tissue perfusion during operation with less depletion of cellular energy stores. The reduction in $\Delta\dot{V}O_2$ during treatment with ketanserin might be especially beneficial in patients with poor myocardial function, as the lower oxygen demand without impairment of myocardial performance improves oxygen balance.

All patients were discharged from the ICU on the first day after operation. However, there was a trend towards a longer duration of ventilatory support in the ketanserin patients. This effect coincided with administration of more fluids later in the ICU. In this study, ketanserin was administered in a standard dose until 18 h after operation, far beyond the period that the patient is at risk of compensatory vasoconstriction. After a longer infusion time, the α_1 adrenergic blocking effect of ketanserin increases and this may explain the lower arterial pressure and administration of more fluids later in the ICU. As it has been shown that ketanserin decreases the lower limit of autoregulation in the kidneys[29], sufficient organ perfusion is likely to be guaranteed at a lower arterial pressure while ketanserin is administered. Titration of ketanserin dose should preferably be based on circulation, and administration of ketanserin can generally be discontinued when the circulation has become stable.

From the preliminary results of this clinical study, we conclude that treatment with i.v. ketanserin, an inhibitor of vasoconstriction, may reduce the degree of endotoxaemia and postoperative hypermetabolism, but does not prevent their occurrence. Low vascular filling was also associated with endotoxaemia. Prevention of endotoxaemia is likely to require a combined strategy aiming at inhibition of vasoconstriction before and during operation using ketanserin and expansion of intravascular volume.

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References

1. Westaby S. Organ dysfunction after cardiopulmonary bypass. A systemic inflammatory reaction by the extracorporeal circuit. *Intensive Care Medicine* 1987; **13**: 89–95
2. Jansen NJG, van Oeveren W, vd Broek L, Oudemans-van Straaten HM, Stoutenbeek CP, Chamg Njoek Joen M, Roozendaal KJ, Eysman L, Wildevuur CRH. Inhibition by dexamethasone of the reperfusion phenomena in cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1991; **102**: 515–525.
3. Chiara O, Giomarelli PP, Biagioli B, Rosi R, Gattinoni L. Hypermetabolic response after hypothermic cardiopulmonary bypass. *Critical Care Medicine* 1987; **15**: 995–1000.
4. Chenoweth DE, Steven WC, Cooper BA, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass. *New England Journal of Medicine* 1981; **304**: 497–503.
5. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pavifico AD. Complement and the damaging effects of cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**: 845–847.
6. van Oeveren W, Kazatchkine MD, Descamps-Latschka B, Maillet F, Fischer E, Carpentier A, Wildevuur CRH. Deleterious effects of cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1985; **89**: 888–899.
7. Oudemans-van Straaten HM, Jansen PGM, te Velthuis H, Beenakkers ICM, Stoutenbeek CP, van Deventer SJH, Sturk A, Eijsman L, Wildevuur ChRH. Increased oxygen consumption after cardiac surgery is associated with the inflammatory response to endotoxaemia. *Intensive Care Medicine* 1996; **22**: 294–300.
8. Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. *New England Journal of Medicine* 1987; **316**: 379–386.
9. Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello ChA, Cerami A, Wolff SM, Wilmore DW. Detection of circulating tumor necrosis factor after endotoxin administration. *New England Journal of Medicine* 1988; **318**: 1481–1486.
10. Fiddian Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Critical Care Medicine* 1987; **15**: 153–156.
11. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and costs. *Intensive Care Medicine* 1994; **20**: 99–104.
12. Anderson L, Landow L, Baek L, Jansen E, Baker S. Association between intramucosal pH and splanchnic endotoxin, antibody to endotoxin and tumor necrosis factor concentrations in patients undergoing cardiopulmonary bypass. *Critical Care Medicine* 1993; **21**: 210–217.
13. Oudemans-van Straaten HM, Jansen PGM, Hoek FJ, van Deventer SJH, Sturk A, Stoutenbeek CP, Tytgat GNJ, Wildevuur ChRH, Eijsman L. Intestinal permeability, circulating endotoxin and post-operative systemic responses in cardiac surgery patients. *Journal of Thoracic and Cardiovascular Anesthesia* 1996; **10**: 187–194.
14. van Reempts J, Borgers M, Xhonneux R, de Clerck F, Awouters F. The inhibition of ischemic lesions of the rat gastric mucosa by a novel serotonin antagonist: a light and electron microscopic study. *Angiology* 1981; **32**: 529–542.
15. Awouters FH, Niemegeers CJ, Janssen PA. A pharmacologic analysis of the rat mast cell 5HT gastric lesion test and the effects of ketanserin. *Drug Development Research* 1985; **5**:303–312.
16. Van Neuten JM, Jansen PAJ, Van Beek J, Xhonneux R, Verbeuren TJ, Vanhoutte P. Vascular effects of ketanserin (R 41 468), a novel antagonist of $5\text{-}HT_2$- serotonergic receptors. *Journal of Pharmacology and Experimental Therapeutics* 1981; **218**: 217–230.

17. Vanhoutte PM, Houston DS. Platelets, endothelium and vasospasm. *Circulation* 1985; 72: 728–734.
18. Jansen, PGM, te Velthuis H, Oudemans-van Straaten HM, Bulder ER, van Deventer SJH, Sturk A, Eijsman L, Wildevuur ChRH. Perfusion-related factors of endotoxin release during cardiopulmonary bypass. *European Journal of Cardiothoracic Surgery* 1994; 8: 125–129.
19. Sturk A, Janssen ME, Muylaert FR, Joop K, Thomas LLM, ten Cate JW. Detection of bacterial toxins with Limulus amoebocyte lysate test. In: Watson SW, Levin J, Novitsky TJ, eds. *Endotoxin Testing in Blood.* New York: Alan R. Liss, 1987; 371–385.
20. Novitsky TJ. Limulus amoebocyte lysate (LAL) detection of endotoxin in human blood. *Journal of Endotoxin Research* 1994; 1: 253–263.
21. Takala J, Keinänen O, Väisänen P, Kari A. Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. *Critical Care Medicine* 1989; 17: 1041–1047.
22. Oudemans-van Straaten HM, Scheffer GJ, Wildevuur ChRH, Eysman L. Oxygen consumption after cardiopulmonary bypass. Implications of different measurement methods. *Intensive Care Medicine* 1993; 19: 105–110.
23. Altman DG. *Practical Statistics for Medical Research.* Glasgow, New York, Tokyo, Melbourne, Madras, London: Chapman and Hall, 1991; 433.
24. Jansen PGM, te Velthuis H, Wildevuur WR, Huybregts MAJM, Bulder ER, van der Spoel HI, Sturk A, Eysman L, Wildevuur ChRH. Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits. *British Journal of Anaesthesia* 1996; 76: 13–19.
25. Reilly PM, Bulkley GB. Vasoactive mediators and splanchnic perfusion. *Critical Care Medicine* 1993; 21 (2) (Suppl): S55–S58.
26. Pogetti RS, Moore FA, Moore EE, Koeike K, Banerjee A. Simultaneous liver and lung injury following gut ischemia is mediated by xanthine oxidase. *Journal of Trauma* 1992; 32: 723–728.
27. Minami K, Körner MM, Vyska K, Kleesiek K, Knobl H, Körfer R. Effects of pulsatile perfusion on plasma catecholamine levels and hemodynamics during and after cardiac operations with cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1990; 99: 82–91.
28. Lameire NH, Matthys E, Kesteloot D, Waterloos MA. Effects of a serotonin blocking agent on renal hemodynamics in the normal rat. *Kidney International* 1990; 38: 823–828.

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Influence of different volume therapy regimens on regulators of the circulation in the critically ill

J. Boldt, M. Mueller, T. Menges, M. Papsdorf and G. Hempelmann

Summary

Various vasoactive substances are involved in the regulation of the macro- and microcirculation. We have investigated if these regulators change during long-term volume therapy with human albumin (HA) or hydroxyethylstarch solution (HES) in trauma and sepsis patients. To maintain pulmonary capillary wedge pressure (PCWP) at 10–15 mm Hg, either 20% HA (HA-trauma, *n*=14; HA-sepsis, *n*=14) or 10% low-molecular weight HES solution (HES-trauma, *n*=14; HES-sepsis, *n*=14) were infused for 5 days, otherwise patient management did not differ between the two groups (trauma/sepsis). Mean arterial pressure (MAP), heart rate (HR), PCWP and cardiac index (CI) were monitored in all patients. Liver function was assessed using the monoethylglycinexylidide (MEGX) test, and gastric intramucosal pH (pH$_i$) was monitored by tonometry to assess splanchnic perfusion. Plasma concentrations of vasopressin, endothelin-1, adrenaline, noradrenaline, atrial natriuretic peptide and 6-keto-prostaglandin $F_{1\alpha}$ were measured from arterial blood samples. All measurements were carried out on the day of admission to the intensive care unit (trauma patients) or on diagnosis of sepsis, and daily over the next 5 days at 12:00. MAP, HR and PCWP did not differ between the corresponding subgroups (trauma/sepsis). CI increased significantly more in the HES than in the HA groups. pH$_i$ and MEGX plasma concentrations did not differ in the trauma patients throughout the study. Both were lower than normal in the sepsis groups and increased more markedly in the HES than in the albumin-treated patients ($P<0.05$). In the trauma patients, concentrations of all vasoactive regulators were very similar in both groups. In both sepsis groups, vasopressors (vasopressin, endothelin-1, noradrenaline and adrenaline) were significantly increased above normal at baseline and decreased more markedly in HES than in HA patients. Concentrations of atrial natriuretic peptide increased only in the HA patients (from 159 (SD 31) to 215 (38) pg ml^{-1} on day 2). Plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ decreased significantly only in the HES sepsis patients (from 112 (25) to 47 (15) pg ml^{-1}). (*Br. J. Anaesth.* 1996;**77**:480–487)

Key words
Intensive care. Fluids, therapy. Fluids, i.v. Polypeptides, cytokines. Sympathetic nervous system, catecholamines.

There are various conditions such as shock, ischaemia, trauma and sepsis that exhibit flow alterations which are inadequate for tissue needs[1]. Various circulating vasoactive substances and inflammatory mediators are important in reducing perfusion in this situation. Activation of the sympathetic nervous system is a compensatory mechanism to maintain peripheral perfusion. Although this neurohumoral activation is beneficial at first, this mechanism becomes deleterious and may be involved in the poor outcome of the critically ill[2]. Recent evidence suggests that the endothelium functions not only as a passive barrier between circulating blood and tissue, but may also be involved in the regulation of microcirculatory blood flow by producing important regulators of vascular tone (e.g. prostaglandins, nitric oxide (NO), endothelins, angiotensin II)[3]. Thus regional regulation of blood flow is a balance between systemic (central) mechanisms (e.g. autonomic nervous system) and other circulating or locally active blood flow regulators.

One approach to improve perfusion in the critically ill is the use of adequate volume replacement. It is necessary not only to guarantee an adequate haemodynamic state but also to avoid microcirculatory abnormalities. Restoration of flow is an essential key for avoiding tissue ischaemia and subsequent development of multiple organ failure (MOF)[4]. Points of controversy in this area appear to be which type of solution is best suited to avoiding the sequelae of trauma or sepsis[5,6]. This controversy refers not only to the crystalloid/colloid debate, but has been widened in recent years to include a colloid/colloid debate as synthetic colloids (e.g. hydroxyethylstarch solutions) have proved to be of benefit for volume

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therapy in this situation[7]. In spite of higher costs, human albumin solutions are still used widely in several centres. Most studies have compared only the short-term effects of volume infusion[8], and evaluation of the efficacy of various volume replacement regimens is not possible with this design. Serial data on the effects of long-term volume therapy with different solutions on regulators of the circulation in the critically ill are lacking. This study was designed to investigate if the type of volume replacement (human albumin *vs* hydroxyethylstarch) influences plasma concentrations of regulators of the circulation.

Patients and methods

After obtaining approval from the Ethics Study Board of the hospital and informed consent from closest relatives, we studied 56 patients from our surgical intensive care unit (ICU). Twenty-eight consecutive trauma patients with an injury severity score (ISS)[9] >15 points and 28 patients with sepsis secondary to major surgery (non-trauma, non-cardiovascular, non-neurosurgery) were prospectively included. Sepsis was defined using the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM)[10], that is more than one of the following criteria: (1) temperature >38 °C or <36 °C; (2) heart rate <90 beat min^{-1}; (3) tachypnoea manifested by ventilatory frequency <20 bpm or Pa_{CO_2} <4.3 kPa; (4) alteration in white blood cell count (>12 000 ml^{-1}, <4000 ml^{-1}, >10% immature neutrophils). Patients with renal insufficiency (serum creatinine >2.0 mg dl^{-1}; blood urea nitrogen >150 mg dl^{-1}; urine output <20 ml h^{-1} in spite of diuretic therapy with frusemide), severe liver dysfunction or disseminated intravascular coagulation were excluded. All patients were haemodynamically stable (mean arterial pressure >70 mm Hg, cardiac index >2.00 litre min^{-1} m^{-1}) before inclusion in the study. The time between surgery and start of the study was more than 12 h. None of the patients was in septic shock before the beginning of the study.

All patients continuously received a mixture of fentanyl and midazolam, and all were receiving controlled mechanical ventilation. FI_{O_2} and ventilatory patterns were adjusted to maintain Pa_{O_2} at 13.33–20 kPa and Pa_{CO_2} at 5.0–6.4 kPa throughout the study.

Prospectively, patients were allocated randomly to one of the following groups: in group I, volume therapy was carried out using 10% low-molecular weight hydroxyethylstarch (HES) solution (mean molecular weight: 200 000 Da, degree of substitution 0.5 (HES-trauma, *n*=14; HES-sepsis, *n*=14); group II, 20% human albumin (HA) was infused for volume therapy (HA-trauma, *n*=14; HA-sepsis, *n*=14).

According to the design of the study, fluid was infused to maintain pulmonary capillary wedge pressure (PCWP) at 10–15 mm Hg. Banked blood cells (RBC) were transfused when haemoglobin (Hb) was <9 g dl^{-1}, fresh frozen plasma (FFP) was given only to maintain haemostasis (prothrombin time <50%; fibrinogen <2 g litre^{-1}) and platelet concentrations were infused when platelet count was <30×10^9 litre^{-1}. Crystalloids (Ringer's solution) were given to all patients to compensate for fluid loss by sweating, gastric tubes, extensive urine output and as a solvent for drugs (e.g. antibiotics).

Dopamine was given in a renal dose of 3 μg kg^{-1} min^{-1} to all patients. Adrenaline was given when mean arterial pressure (MAP) was <60 mm Hg and cardiac index (CI) was <2.25 litre min^{-1} m^{-2}. Noradrenaline was administered when MAP was <60 mm Hg and systemic vascular resistance (SVR) was <600 dyn s^{-1} cm^{-5} (target: MAP >70 mm Hg). All additional therapy (parenteral feeding, antibiotics, pharmacological support, ventilation) was performed according to our standard procedure of management of intensive care patients by physicians who were not involved in the study and who were blinded to the grouping of the patients (HA *vs* HES).

Heart rate (HR), MAP, pulmonary capillary wedge pressure (PCWP) and CI (by the thermodilution technique) were monitored in all patients.

Arterial blood samples were obtained from an indwelling arterial cannula and plasma was separated immediately and stored at −30 °C. Endothelin-1 (ET-1) was measured by radioimmunoassay (RIA; Biocode, Sclessin, Belgium)[11]. Sensitivity of the test kit is 0.5 pg ml^{-1}; cross reactivity with endothelin-1 is 100%, endothelin-2 34%, endothelin-3 64%, big-endothelin 2% and other vasoactive peptides (e.g. angiotensin I and II, bradykinin, atrial natriuretic peptide) <0.1%. Vasopressin (by RIA; Instar Corp., Stillwater, MN, USA[12]), atrial natriuretic peptide (ANP) (by RIA; Instar Corp.[13]), catecholamine plasma concentrations (adrenaline and noradrenaline by high-pressure liquid chromatography with combined electrochemical detection), and 6-ketoprostaglandin $F_{1\alpha}$ (the stable but inactive end-product of prostaglandin I_2 (prostacyclin), using a commercially available enzyme immunoassay kit (TiterZyme, PerSeptive Diagnostics, Cambridge, MA, USA))[14] were measured from plasma within 2 months after blood sampling. All data are means of duplicate measurements, and data were obtained by one investigator who was blinded to the patients (trauma/sepsis) and their grouping (HA/HES). When data differed by more than 10%, the measurement was repeated and the mean value calculated.

Gastric intramucosal pH (pH_i) was measured using a nasogastric tube (Tonometer, Tonometrics, Worcester, MA, USA). An equilibration time of 60 min was used, and pH_i was measured according to the guidelines of the manufacturer. Gastric pH_i was calculated using the Henderson–Hasselbalch equation[15].

Liver function was assessed using the monoethylglycinexylidide (MEGX) test. MEGX was measured from arterial blood samples by high-pressure liquid chromatography before and 15 min after lignocaine 1 mg kg^{-1} i.v.[16]. An MEGX plasma concentration of <50 ng ml^{-1} was taken as indicating abnormal liver function.

All measurements were carried out on the day of admission (traumatized patients) or on the day of sepsis diagnosis (baseline values) and continued for the following 5 days at 12:00.

All variables are expressed as mean (SD). Groups were compared using the Mann–Whitney *U* test. One- and two-way analysis of variance (ANOVA) with repeated measures (including Scheffé's test)

Table 1 Patient characteristics and data from intensive care management (mean (SD or range) or number). HES = hydroxyethylstarch solution; HA = human albumin; ISS = injury severity score. * $P < 0.05$ compared with corresponding group

	HES-trauma (n=14)	HA-trauma (n=14)	HES-sepsis (n=14)	HA-sepsis (n=14)
Age (yr)	40.9 (22–55)	37.2 (19–60)	62.1 (45–71)*	62.3 (51–70)*
Weight (kg)	75.1 (10.9)	78.8 (11.1)	73.3 (10.5)	79.3 (11.9)
Type of surgery				
Bone	14	14	—	—
Abdominal	6	5	10	9
Thoracic	3	2	2	3
Combined	—	1	3	3
Non-survival (n)				
During the study	2	3	4	4
After the study	1	—	2	3
Scoring at baseline				
ISS	23.0 (4.9)	22.1 (5.4)	—	—
APACHE II	15.9 (2.8)	16.8 (3.1)	21.1 (3.6)*	20.3 (3.9)*
Catecholamine support (n)				
Adrenaline (μg min^{-1})	2 (4–6)	3 (5–10)	11 (5–15)	12 (5–20)
Noradrenaline (μg min^{-1})	1 (5–10)	2 (5–10)	6 (5–15)	7 (5–15)
Dopamine (μg min^{-1})	14 (200–300)	14 (200–280)	14 (220–290)	14 (210–300)

were used to determine the effects of group, time and group–time interactions for each variable. P<0.05 was considered significant.

Results

Patients in the two subgroups (trauma/sepsis) were similar in characteristics and intensive care therapy (table 1). ISS, APACHE II score and outcome were similar in the corresponding groups. The number of patients who died during (early non-survivors) and after (late non-survivors) the study was comparable in the corresponding volume groups (trauma/sepsis) (table 1). All of these patients died from multiple organ dysfunction syndrome (MODS). Use of blood, FFP, amount of crystalloids and fluid balance did not differ between the groups (table 2). In both trauma and sepsis patients, significantly more HES than HA was infused during the study (table 2). HES costs approximately £9 per 500 ml whereas HA costs approximately £45 per 100 ml. Volume replacement with HA was significantly more costly than with HES (cumulative costs: HES-trauma, £77 (13); HES-sepsis, £70 (13); HA-trauma, £936 (156); HA-sepsis, £869 (200)). Catecholamine support was necessary more often and in higher doses in the sepsis compared with the trauma patients, but there were no differences between the two sepsis groups. Blood and urine electrolyte concentrations, haemoglobin, temperature and renal function did not differ significantly between the two corresponding groups.

MAP, HR, PCWP, CI and pulmonary function (Pa_{O_2}/FI_{O_2}) at baseline did not differ in the trauma and sepsis groups (table 3). CI increased significantly more in HES- than in HA-treated patients (table 3).

Table 2 APACHE II score and cumulative volume therapy during the study (mean (SD)). HES = hydroxyethylstarch solution (cost approximately £9 per 500 ml); HA = human albumin (cost approximately £45 per 100 ml); crystalloids = all crystalloid solutions; PRC = packed red blood cells; FFP = fresh frozen plasma. * $P < 0.05$ different from other groups

		Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
APACHE II score (points)	HES-trauma	15.9 (2.8)	16.4 (2.9)	16.0 (2.9)	13.9 (2.9)	14.1 (2.7)	14.8 (2.8)
	HA-trauma	16.8 (3.1)	17.2 (2.5)	17.1 (4.1)	15.0 (2.3)	15.1 (2.4)	14.5 (2.1)
	HES-sepsis	21.1 (3.6)	22.0 (3.1)	20.3 (3.3)	19.0 (2.3)	15.1 (3.3)	15.0 (2.7)
	HA-sepsis	20.2 (3.9)	21.9 (3.9)	22.4 (3.0)	20.1 (3.1)	17.2 (4.2)	18.3 (3.4)
HES (ml) (cumulative)	HES-trauma	—	1050 (200)	1700 (400)	2600 (500)	3650 (550)	4300 (750)
	HES-sepsis	—	800 (200)	1750 (450)	2650 (650)	3050 (500)	3950 (750)
HA (ml) (cumulative)	HA-trauma	—	600 (200)	950 (250)	1350 (250)	1900 (400)	2100 (350)
	HA-sepsis	—	450 (150)	800 (250)	1250 (300)	1550 (350)	1950 (400)
Crystalloids (litre) (cumulative)	HES-trauma	—	3.0 (0.8)	4.5 (1.5)	8.5 (2.0)	11.0 (3.0)	14.5 (4.5)
	HA-trauma	—	2.5 (1.0)	5.0 (2.0)	9.0 (2.5)	12.5 (3.5)	15.3 (3.5)
	HES-sepsis	—	3.8 (1.2)	6.3 (1.3)	10.5 (3.5)	12.5 (3.5)	15.9 (2.5)
	HA-sepsis	—	3.2 (0.9)	7.0 (2.2)	10.3 (2.5)	13.0 (4.8)	16.6 (3.0)
PRBC (no. patients/no. units)	HES-trauma	—	11/25	6/15	5/10	4/12	3/8
	HA-trauma	—	10/22	7/14	4/15	3/10	3/10
	HES-sepsis	—	6/10	4/10	4/8	2/4	2/4
	HA-sepsis	—	4/13	3/12	4/8	2/6	3/4
FFP (no. patients/no. units)	HES-trauma	—	5/12	2/6	4/10	3/4	2/4
	HA-trauma	—	5/11	3/6	3/12	2/8	2/4
	HES-sepsis	—	4/14	3/10	2/8	2/8	2/6
	HA-sepsis	—	4/15	3/9	2/4	2/9	2/4

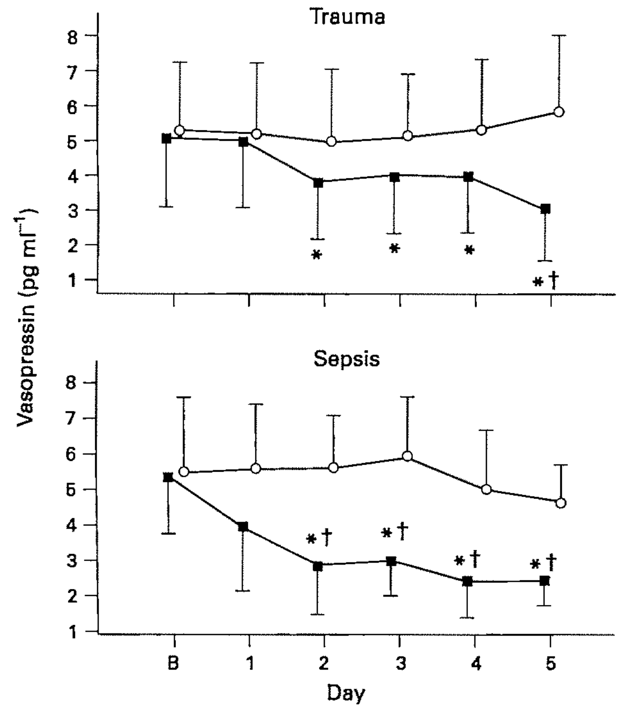

Figure 1 Changes in plasma concentrations of vasopressin (normal range <3.0 pg ml^{-1}) in the trauma and sepsis patients after administration of HES (■) or albumin (○). B=Baseline. †P<0.05 compared with baseline; *P<0.05 compared with corresponding volume group.

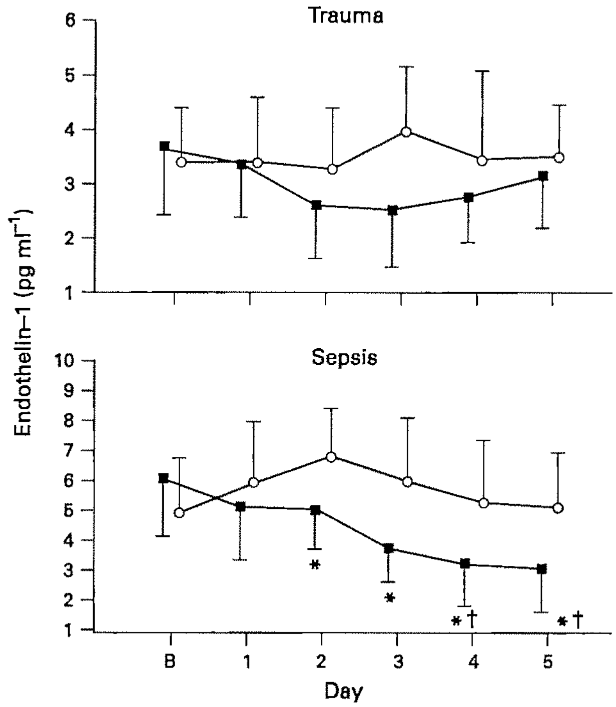

Figure 2 Changes in plasma concentrations of endothelin-1 (normal range <3 pg ml^{-1}) in the trauma and sepsis patients after administration of HES (■) or albumin (○). B=Baseline. †P<0.05 compared with baseline; *P<0.05 compared with corresponding volume group.

Pa_{O_2}/Fi_{O_2} increased in the trauma and sepsis groups in which HES was infused, whereas it was almost unchanged in the albumin-treated patients, being significantly different compared with the corresponding HES-group at the end of the study (table 3).

At baseline, plasma concentrations of MEGX were significantly lower in sepsis than in trauma patients (table 3). In the trauma patients, they remained almost unchanged and did not differ between the two groups. In the sepsis patients, plasma concentration of MEGX increased earlier in HES- than in HA-treated patients (table 3).

pH_i did not differ in the trauma patients throughout the study (table 3). In the sepsis patients it was

Table 3 Mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), monoethylglycinexylidide (MEGX) test and intramucosal pH (pH_i) in the different groups (mean (SD)). † $P < 0.05$ compared with baseline value; * $P < 0.05$ compared with corresponding group

		Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
MAP (mm Hg)	HES-trauma	70.9 (10.1)	80.2 (12.1)	78.9 (10.3)	79.1 (12.0)	80.1 (12.2)	80.2 (9.8)
	HA-trauma	72.1 (11.1)	80.1 (10.5)	80.2 (11.1)	80.2 (11.0)	78.1 (9.8)	78.2 (11.1)
	HES-sepsis	70.1 (9.6)	74.3 (9.7)	79.3 (11.2)	80.0 (12.6)	80.2 (12.8)	82.1 (11.5)
	HA-sepsis	77.9 (10.1)	77.1 (11.1)	76.4 (11.2)	77.4 (9.6)	77.0 (12.1)	79.2 (12.5)
PCWP (mm Hg)	HES-trauma	11 (2)	14 (3)	14 (2)	14 (3)	14 (3)	14 (2)
	HA-trauma	10 (2)	13 (3)	13 (3)	14 (3)	13 (2)	15 (2)
	HES-sepsis	10 (3)	14 (2)	14 (2)	14 (3)	15 (3)	14 (1)
	HA-sepsis	10 (2)	14 (2)	13 (3)	13 (3)	14 (2)	15 (2)
CI (litre min^{-1} m^{-2})	HES-trauma	3.33 (0.5)	4.65 (0.5)†*	4.76 (0.4)†*	4.65 (0.5)†*	4.60 (0.6)†*	4.35 (0.5)†
	HA-trauma	3.25 (0.4)	4.01 (0.7)	4.02 (0.6)	4.26 (0.6)	4.02 (0.7)	4.11 (0.4)
	HES-sepsis	4.01 (0.7)	5.52 (0.7)†*	5.32 (0.6)†*	5.54 (0.7)†*	5.77 (0.7)†*	5.79 (0.9)†*
	HA-sepsis	3.87 (0.6)	4.11 (0.6)	4.05 (0.8)	4.03 (0.6)	4.39 (0.7)	4.77 (0.7)
Pa_{O_2}/Fi_{O_2} (mm Hg)	HES-trauma	275 (79)	338 (63)	326 (66)	327 (81)	355 (67)*	352 (67)*
	HA-trauma	257 (65)	322 (45)	321 (85)	319 (61)	284 (67)	289 (66)
	HES-sepsis	239 (66)	265 (56)	299 (59)	309 (67)	343 (62)*	337 (56)*
	HA-sepsis	234 (80)	267 (64)	250 (79)	230 (50)	252 (65)	256 (49)
MEGX (ng ml^{-1})	HES-trauma	55.0 (19.2)	62.4 (18.8)	64.6 (20.1)	64.5 (15.7)	57.5 (18.0)	55.4 (16.5)
	HA-trauma	59.9 (21.9)	54.5 (16.6)	53.4 (16.6)	56.6 (22.2)	56.0 (16.3)	56.9 (16.0)
	HES-sepsis	29.3 (14.3)	33.5 (15.5)	47.9 (14.9)†*	49.5 (18.9)†*	49.4 (8.9)†*	49.6 (14.5)†
	HA-sepsis	27.0 (12.3)	24.9 (12.7)	33.3 (16.6)	34.4 (13.3)	44.0 (13.1)†*	48.7 (15.2)†
pH_i	HES-trauma	7.37 (0.14)	7.40 (0.13)	7.46 (0.12)	7.45 (0.11)	7.43 (0.11)	7.39 (0.13)
	HA-trauma	7.36 (0.11)	7.38 (0.14)	7.40 (0.15)	7.39 (0.14)	7.41 (0.15)	7.41 (0.15)
	HES-sepsis	7.25 (0.14)	7.33 (0.13)	7.41 (0.16)†*	7.42 (0.16)†*	7.48 (0.14)†*	7.46 (0.15)†*
	HA-sepsis	7.27 (0.12)	7.30 (0.12)	7.25 (0.16)	7.26 (0.15)	7.28 (0.12)	7.26 (0.10)

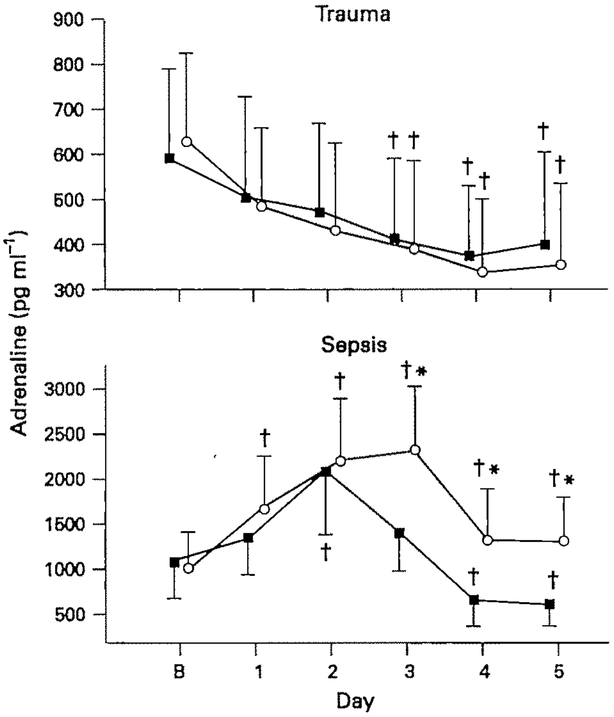

Figure 3 Changes in plasma concentrations of adrenaline (normal range 30–85 pg ml^{-1}) in the trauma and sepsis patients after administration of HES (■) or albumin (○). B=Baseline. †$P<0.05$ compared with baseline; *$P<0.05$ compared with corresponding volume group.

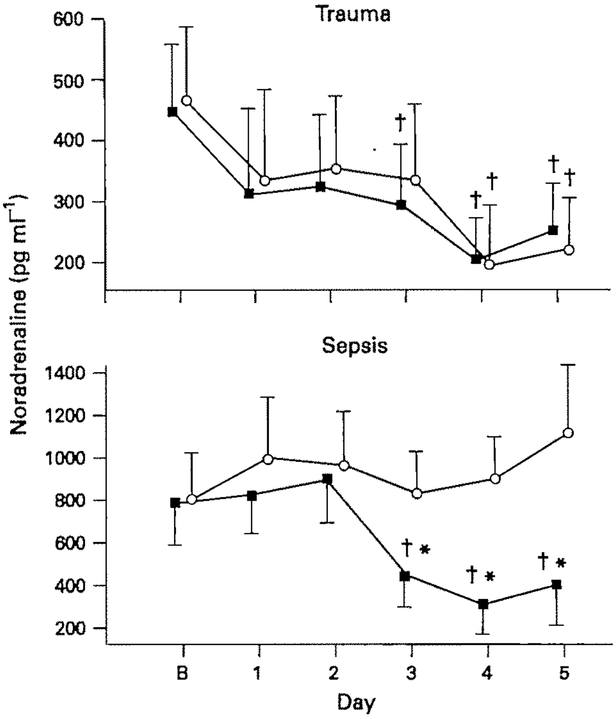

Figure 4 Changes in plasma concentrations of noradrenaline (normal range 180–250 pg ml^{-1}) in the trauma and sepsis patients after administration of HES (■) or albumin (○). B=Baseline. †$P<0.05$ compared with baseline; *$P<0.05$ compared with corresponding volume group.

similar at baseline (<7.30) and increased only in the HES group (to 7.48).

Vasopressin plasma concentrations were increased at baseline in all patients (>3.0 pg ml^{-1}) (fig. 1). Concentrations decreased to almost normal values in HES-treated patients but remained increased in both albumin groups. ET-1 plasma concentrations were within the normal range in trauma patients and did not differ between the two groups (fig. 2). In the sepsis patients, ET-1 plasma concentrations decreased in the HES group being significantly lower than in the albumin-treated patients at the end of the investigation.

Plasma concentrations of adrenaline and noradrenaline decreased similarly in all trauma patients

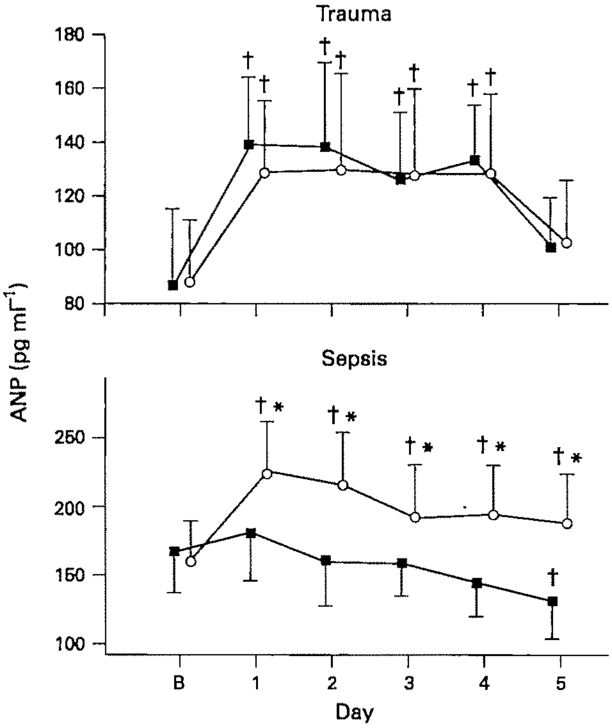

Figure 5 Changes in plasma concentrations of atrial natriuretic peptide (ANP) (normal values 20–100 pg ml^{-1}) in the trauma and sepsis patients after administration of HES (■) or albumin (○). B=Baseline. †$P<0.05$ compared with baseline; *$P<0.05$ compared with corresponding volume group.

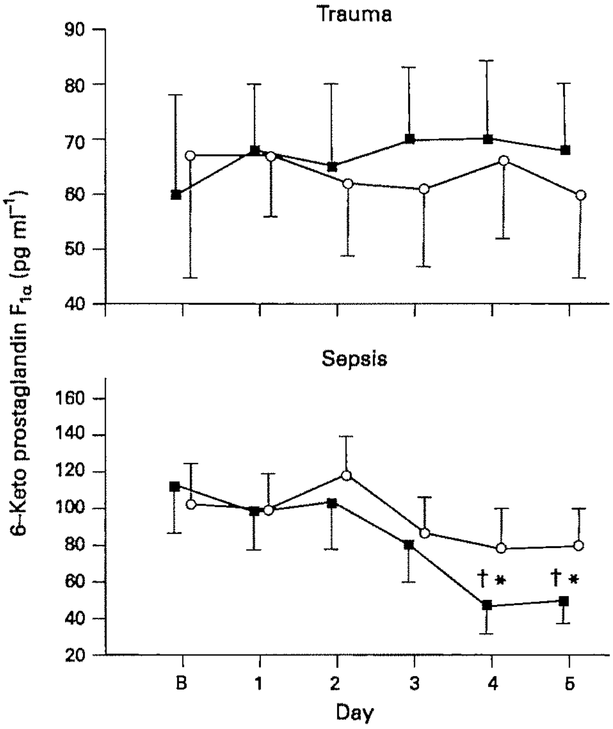

Figure 6 Changes in plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ (normal range <30 pg ml^{-1}) in the trauma and sepsis patients after administration of HES (■) or albumin (○). B=Baseline. †$P<0.05$ compared with baseline; *$P<0.05$ compared with corresponding volume group.

($P<0.05$) (figs 3, 4). In the sepsis patients, concentrations decreased significantly only in the HES group until the end of the study. In the albumin group, adrenaline increased, whereas noradrenaline remained unchanged during the study. Atrial natriuretic factor increased similarly to greater than normal values in both sepsis groups and did not reach normal values at the end of the study (fig. 5). In the albumin group, plasma concentrations were increased at the start of the study and increased further (215.5 (38.9) pg ml^{-1} on day 2), whereas they were decreased in HES patients (131.3 (28.8) pg ml^{-1} on day 5). Plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ did not differ in the trauma groups (fig. 6). In the sepsis patients, concentrations decreased more in the HES group (from 112 (25) to 47 (15) pg ml^{-1}) ($P<0.05$ *vs* HA-patients).

Discussion

Both trauma and sepsis may impair vasoregulation which is needed to control the distribution of cardiac output. Current evidence suggests that systemic and endothelial-derived mediators generated in critical illness may precipitate or sustain disturbances in tissue blood supply. Microcirculatory disturbances appear to be of major importance for the development of, and progression in the pathophysiology of shock or the evolution of MOF[4]. In this situation, volume infusion is known to be therapeutic. One important objective of fluid therapy is to restore or guarantee tissue perfusion. Whether one fluid is better than another may be a result of different experimental designs and end-points of volume therapy. To understand the effects of varying fluid management it is necessary not to limit the investigation to a specific number of hours after single volume infusion. Thus we studied the effects of two different volume therapy regimens over a period of 5 days.

In our sepsis patients, plasma concentrations of important regulators of the macro- and microcirculation were significantly more altered than in our trauma groups. Vasopressin, ET1, adrenaline and noradrenaline plasma concentrations exceeded the normal range at baseline. The increased concentrations of these potent vasoconstrictors may cause microcirculatory alterations, inadequate perfusion and ultimately tissue damage. This compensatory activation of the vasopressor systems is beneficial at first, but may become deleterious. It may result in splanchnic vasoconstriction, although there is a marked increase in the need for oxygen delivery in this situation[17]. In this study, pH_i differed between our sepsis (<7.30) and trauma (>7.35) patients, indicating alteration in splanchnic perfusion in sepsis[18]. Also the MEGX test was reduced below the normal range (<50 ng ml^{-1}) in our sepsis patients, indicating altered hepatic function, possibly because of perfusion deficits. The increased plasma concentrations of potent systemic and local vasodilators (ANP and 6-keto-prostaglandin $F_{1\alpha}$) in our sepsis patients may be regarded as a compensatory reaction to activation of the vasopressor systems.

ET-1 represents an extremely potent vasoconstrictor, which may play an important role in (regional) blood flow regulation[19]. ET-1 is released by pathophysiological states that are characterized by limitation of cardiac output or hypotension. Moreover, endotoxin directly stimulates ET-1 release *in vivo* and *in vitro*[20]. In sepsis patients, the greatest severity of disease paralleled the highest concentration of ET-1[21]. One problem with measurement of ET-1 from plasma samples is that it does not represent the actual local concentration, but appears to be a "spill over" of endothelin released by the endothelium.

The sympathetic nervous system is activated in the critically ill[22]. The increased plasma concentrations of catecholamines in this study reflected this activation. The higher plasma concentrations in our sepsis patients may also be related to the higher catecholamine support in these patients. However, inotropic support (adrenaline) and vasopressor therapy (noradrenaline) did not differ in our sepsis groups and thus cannot explain the differences between the two volume groups. ANP plays an important role in the regulation of arterial pressure and volume homeostasis. Plasma concentrations of ANP were reported to be increased significantly from normal in sepsis patients, particularly in combination with acute respiratory failure[23]. Nakae and colleagues[24] showed that 6-keto-prostaglandin $F_{1\alpha}$ was higher in sepsis patients who died than in those who survived, and it may serve as a marker of illness severity.

It has been shown from animal and human studies that adrenaline stimulates ANP secretion[25], by which negative effects on the (micro-) circulation of adrenaline may be compensated. ET-1 may stimulate the release of catecholamines and renin[26], thus possibly contributing to vasconstriction and reduced blood flow at the microcirculatory level. In contrast, ET increased circulating ANP in dogs and ANP acts as a potent inhibitor of ET synthesis. Thus ANP may function as a negative feedback regulator of ET[5] and the vasoconstrictive actions of endothelin are opposed by this vasodilator[27]. Also, prostaglandin synthesis was shown to be increased by adrenaline[28], by which counter regulatory vasodilatation may be induced.

In our trauma patients, the choice of volume therapy did not influence either the measured regulators of the circulation, pH_i or the MEGX test. This implies that volume therapy with 20% HA in these patients can be replaced easily by HES. In our sepsis patients, however, long-term volume therapy for 5 days with hydroxethylstarch solution resulted in a more beneficial influence overall on these regulators than infusion of albumin. pH_i and the MEGX test improved also more markedly in the HES than in the HA group. As monitoring of pH_i has been shown to be an excellent indicator of changes in splanchnic perfusion[15 18], improved splanchnic perfusion may be assumed in HES patients. We used the MEGX test in this study to assess hepatic function because it was demonstrated in animal experiments that this test is a suitable tool for clinical evaluation and therapeutic interventions after hypovolaemic shock[16]. The increase in MEGX plasma concentrations in our sepsis patients treated with HES solution indicated compensation of possible hepatic perfusion deficits. Overall, HES-treated patients also showed better oxygenation than HA-treated patients. This may result from either improved microcirculation in the pulmonary circulation or from less shift of fluid from the intravascular to the interstitial space resulting in less extravascular lung water (EVLW).

The reasons for these differences between the two volume regimens can only be speculative at present; although fluid balance and PCWP did not differ significantly between the corresponding groups throughout the study, higher preload with subsequent improved systemic perfusion (increased CI) in the HES groups cannot be excluded as a reason for the reduction in circulating vasopressors. Beneficial rheological effects secondary to the HES solution may have improved the microcirculation and tissue perfusion and may thus have resulted in less activation of vasopressor systems. Direct effects on endothelial cells may also have played a role; 10% pentastarch (a comparable low-molecular weight HES preparation) may have influenced directly endothelial function, for example by beneficially altering endothelial cell integrity by oxygen free radical scavenging or by stabilizing fragile cell membranes[29]. In an experimental setting, Schmand and colleagues[30] found that in a group of animals which had received HES solution for volume replacement, circulating interleukin-6 (IL-6) concentrations were normalized. This is of great interest as IL-6 may be detrimental to host immune function and thus may also be involved in (micro-) circulatory abnormalities.

Changes in pulmonary function, pH$_i$ and liver function (assessed by the MEGX test) were influenced more beneficially in those patients in whom HES was infused in comparison with HA-treated patients. Survival rate during the study and thereafter was similar in the two groups. Effective fluid therapy appears to be the mainstay of managing the critically ill; however, it was not the aim of this study to clarify if the choice of fluid has an impact on patient outcome. Large studies with considerable numbers of patients must be undertaken to fully evaluate the influence of volume regimen on outcome.

References

1. Intaglietta M. Objectives for the treatment of the microcirculation in ischaemia, shock, and reperfusion. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*. Berlin, Heidelberg, New York: Springer, 1990; 293–298.
2. Turnbull AV, Little RA. Neuro-hormonal regulation after trauma. Circulating cytokines may also contribute to an activated sympathetic–adrenal control. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*. Berlin, Heidelberg, New York, Tokyo: Springer, 1993; 574–581.
3. Brenner BM, Troy JL, Ballermann B. Endothelium-dependent vascular responses. *Journal of Clinical Investigation* 1989; **84**: 1373–1378.
4. Lewis DH. The effects of multiple organ failure on the regulation of the circulation with special reference to the microcirculation. In: Manabe H, Zweifach BW, Messmer K, eds. *Microcirculation in Circulatory Disorders*. Tokyo, Berlin, Heidelberg: Springer, 1988; 103–108.
5. Prough DS, Johnston WE. Fluid restoration in septic shock: no solution yet. *Anesthesia and Analgesia* 1989; **69**: 699–704.
6. Davidson I. Fluid resuscitation of shock: current controversies. *Critical Care Medicine* 1989; **17**: 1078–1080.
7. Edwards JD, Nightingale P, Wilkins RG, Faragher EB. Hemodynamic and oxygen transport response to modified fluid gelatin in critically ill patients. *Critical Care Medicine* 1988; **17**: 996–998.
8. Beards SC, Watt T, Edwards JD, Nightingale P, Farragher EB. Comparison of the hemodynamic and oxygen transport responses to modified fluid gelatin and hetastarch in critically ill patients: a prospective, randomized trial. *Critical Care Medicine* 1994; **22**: 600–605.
9. Baker SP, O'Neill B. The injury severity score: an update. *Journal of Trauma* 1976; **16**: 882–888.
10. Members of the American College of Chest Physicians/Society of Critical Care Medicine Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Critical Care Medicine* 1992; **20**: 864–874.
11. Xuan YT, Whorton AR, Shearer-Poor E, Boyd J, Watkins WD. Determination of immunoreactive endothelin in medium from cultured endothelial cells and human plasma. *Biochemical and Biophysical Research Communications* 1989; **164**: 326–332.
12. Pullan PT, Clappison BH, Johnston CI. Plasma vasopressin and human neurophysins in physiological and pathophysiological states associated with changes in vasopressin secretion. *Journal of Clinical Endocrinology Metabolism* 1979; **49**: 580–587.
13. Kross J, Dries DJ, Kumar P, Bakhos M, Mathru M. Atrial natriuretic peptide may not play a role in diuresis and natriuresis after cardiac operations. *Journal of Thoracic and Cardiovascular Surgery* 1992; **103**: 1168–1171.
14. Morris HG, Sherman NA, Shepperdson FT. Variables associated with radioimmunoassay of prostaglandins in plasma. *Prostaglandins* 1981; **21**: 771–787.
15. Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *British Journal of Anaesthesia* 1995; **74**: 591–606.
16. Chandel B, Shapiro MJ, Kurtz M, Rana WU, Matthews M, Jellinek M, Baue AE. MEGX (monoethylglycinexylidide) test: a novel in vivo test to measure early hepatic dysfunction after hypovolemic shock. *Shock* 1995; **3**: 51–53.
17. McNeill JR, Stark RD, Greeway CV. Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. *American Journal of Physiology* 1970; **219**: 1342–1347.
18. Gutierrez G, Bismar H, Dantzker DR, Silva N. Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. *Critical Care Medicine* 1992; **20**: 451–457.
19. Yanagisawa M, Kurihara H, Kimura S. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature (London)* 1988; **322**: 411–415.
20. Sugiura M, Inagami T, Kon V. Endotoxin stimulates endothelin-release in vivo and in vitro as determined by radioimmunoassay. *Biochemical and Biophysical Research Communications* 1989; **161**: 1220–1222.
21. Pittet JF, Morel DR, Hemsen A, Gunning, Lacroix JS, Suter PM, Lundberg JM. Elevated endothelin-1 concentrations are associated with severity of illness in patients with sepsis. *Annals of Surgery* 1991; **213**: 261–264.
22. Hall RC, Hodge RL. Vasoactive hormones in endotoxin shock: a comparative study in cats and dogs. *Journal of Physiology (London)* 1971; **213**: 69–84.
23. Mitaka C, Nagura T, Sakaishi N, Tsunoda Y, Toyooka H. Plasma alpha-atrial natriuretic peptide concentrations in acute respiratory failure with sepsis: preliminary study. *Critical Care Medicine* 1990; **18**: 1201–1207.
24. Nakae H, Endo S, Inada K, Watanabe M, Baba N, Yoshida M. Relationship between leukotriene B4 and prostaglandin IV-2V in patients with sepsis. *Research Communications of Molecular Pathology and Pharmacology* 1994; **86**: 37–42.
25. Rushkoaho H, Lang RE, Toth M, Ganten D, Unger T. Release and regulation of atrial natriuretic peptide (ANP). *European Heart Journal* 1987; **8** (Suppl. B): 99–109.
26. Boarder MR, Marriott DB. Characterization of endothelin-1 stimulation of catecholamine release from adrenal chromaffin cells. *Journal of Cardiovascular Pharmacology* 1989; **13** (Suppl. 5): S223–S224.
27. Goetz KL, Wang BC, Madwed JB, Zhu JL, Leadley RJJ. Cardiovascular, renal, and endocrine responses to intravenous endothelin in conscious dogs. *American Journal of Physiology* 1988; **255**: R1064–R1068.
28. Herman CA, Martinez JM. Epinephrine stimulates prostaglandin synthesis by bullfrog lung from warm-acclimated, but not cold-climated, animal. *Journal of Experimental Zoology* 1988; **248**: 101–108.
29. van der Heide RS, Sobotka PA, Gronte CE. Effects of the free radical scavenger DMTU and mannitol on the oxygen paradox in perfused rat hearts. *Journal of Molecular and Cellu-*

lar Cardiology 1987; **19**: 619.

30. Schmand JF, Ayala A, Morrison MH, Chaudry IH. Effects of hydroxyethyl starch after trauma–hemorrhage shock: restoration of macrophage integrity and prevention of increased circulating interleukin-6 level. *Critical Care Medicine* 1995; **23**: 806–814.

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Potency and time course of action of rocuronium during desflurane and isoflurane anaesthesia

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Summary

We have studied the potency and onset and duration of action of rocuronium in patients anaesthetized with 1 MAC of desflurane or isoflurane (in 66% nitrous oxide). Potency was estimated using the single bolus dose technique. Neuromuscular block was measured by stimulation of the ulnar nerve and recording the force of contraction of the adductor pollicis muscle. The ED_{50} and ED_{95} of rocuronium were estimated as 138 (95% confidence limits 117–162) μg kg^{-1} and 281 (241–328) μg kg^{-1}, and 126 (105–151) μg kg^{-1} and 283 (236–339) μg kg^{-1} during desflurane and isoflurane anaesthesia, respectively. The mean times to onset of maximum block after rocuronium 0.6 mg kg^{-1} were 1.0 (SD 0.10) min and 1.1 (0.15) min, respectively, during anaesthesia with desflurane and isoflurane. The respective times to recovery of T1 (the first response in the train-of-four (TOF) stimulation) to 25% and 90% were 36 (8.3) min and 54 (15.4) min during desflurane anaesthesia and 31 (8.2) min and 45 (12.7) min during isoflurane anaesthesia. The times to recovery of the TOF ratio to 0.7 were 66 (13.4) min and 52 (16.3) min and the 25–75% recovery indices 14 (5.3) min and 10 (3.2) min, respectively, in the desflurane and isoflurane groups. There were no differences in the estimated potency or onset of action of rocuronium during desflurane and isoflurane anaesthesia. However, duration of action tended to be longer during desflurane anaesthesia although only the differences in times to TOF ratio of 0.7 and the recovery indices were close to being significantly different (P=0.0503 and 0.0560). (*Br. J. Anaesth.* 1996;**77**:488–491)

Key words

Neuromuscular block, rocuronium. Anaesthetics volatile, desflurane. Anaesthetics volatile, isoflurane. Neuromuscular block, measurement of response. Potency, anaesthetic, ED_{50}.

Desflurane is a new volatile agent with a low blood-gas solubility giving it the properties of rapid uptake and elimination[1]. Rocuronium is a newer aminosteroid non-depolarizing neuromuscular blocker with a rapid onset and intermediate duration of action[2 3]. Although there are some reports of interaction of neuromuscular blockers with desflurane[4–6], this is not known for rocuronium. Most of these studies have involved studying the effects of only single doses of neuromuscular blockers. This study was undertaken to compare the potency and time course of action of rocuronium during anaesthesia with desflurane or isoflurane.

Patients and methods

We studied 68 patients, aged 18–65 yr, ASA I or II, with their written informed consent and approval of the Research Ethics Committee. Exclusion criteria were body weight greater or less than 30% of ideal for height and patients receiving medication known to interact with neuromuscular blocking drugs.

After premedication with temazepam 10–20 mg, anaesthesia was induced with fentanyl 2 μg kg^{-1} and propofol 2–3 mg kg^{-1}, and maintained with either isoflurane or desflurane and 66% nitrous oxide in oxygen, based on a computer-generated randomization scheme. Ventilation of the lungs was assisted to maintain normocapnia and skin temperature over the adductor pollicis was maintained greater than 32 °C. End-tidal concentration of volatile agent was monitored using the Ohmeda 5250 respiratory gas monitor and stabilized at 1 MAC (adjusted for age and concomitant use of nitrous oxide; 4% and 2.8% desflurane, and 0.56% and 0.5% isoflurane for those aged 18–30 yr and 31–65 yr, respectively)[7 8].

Heart rate, arterial pressure and oxygen saturation were monitored in a standard way. The ulnar nerve was stimulated transcutaneously at the wrist with supramaximal stimuli of 0.2 ms duration in a single twitch mode at 0.1 Hz for potency estimation and in a train-of-four (TOF) mode at 2 Hz every 12 s for the onset and duration of action part of the study. The resultant force of contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd, Denmark). Baseline neuromuscular responses were allowed to stabilize at the same time as the end-tidal concentration of the volatile agent was being stabilized over a period of about 10 min.

We studied 48 patients for estimation of potency using the single bolus technique, described in previous studies and preferred for neuromuscular block-

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ers with intermediate duration of action[9 10]. Twelve patients each (six for desflurane and six for isoflurane) were allocated randomly to receive rocuronium 75, 150, 225 or 300 µg kg^{-1}. Maximum block attained with each dose was recorded and the study terminated. Subsequently, anaesthesia was carried out as appropriate for surgical needs. Twitch height data were subjected to arc-sine transformation[11]. Dose–response curves were constructed using least squares regression analysis and subjected to analysis of covariance. ED_{50} and ED_{95} (doses required to produce 50% and 95% depression of twitch response, respectively) were estimated from the results.

A separate group of 20 patients (10 each in the desflurane and isoflurane groups) anaesthetized in the same way as above was studied to measure the onset and duration of action of rocuronium 0.6 mg kg^{-1}. The variables recorded were onset time (time from drug administration to maximum effect), and times to recovery of T1 to 25% and 90% of control, and of the TOF ratio to 0.7. The results of this part of the study were analysed using the *t* test. $P<0.05$ was considered significant.

Results

The groups were comparable in age, weight, height and sex distribution (table 1). Mean maximum twitch depression attained with each dose of rocuronium is given in table 2; mean values ranged from 14% and 25% with desflurane and isoflurane, respectively, with a dose of rocuronium 75 µg kg^{-1}, to 97% and 99% with the 300-µg kg^{-1} dose. The degree of block was dose-related but the difference between groups for each of the doses was not significant.

The dose–response curves (fig. 1) did not differ in their slopes or intercepts. The calculated ED_{50} and ED_{95} values are given in table 3. These were similar and almost identical: 138 (95% confidence intervals 117–162) µg kg^{-1} and 126 (105–151) µg kg^{-1}, and 281 (241–328) and 283 (236–339) µg kg^{-1}, respectively, during desflurane and isoflurane anaesthesia.

The times for onset and duration of action of rocuronium 0.6 mg kg^{-1} are given in table 4. Onset times were 1 and 1.1 min in the desflurane and isoflurane groups, respectively (ns). Times to 25% recovery of T1 were 36 and 31 min, to T1 of 90% 54 and 45 min, and to TOF ratio of 0.7, 66 and 52 min in the desflurane and isoflurane groups, respectively. The 25–75% recovery indices were 14 and 10 min, respectively, in the desflurane and isoflurane groups. Although recovery times to all end-points were longer in the desflurane group, only the times for TOF ratios to reach 0.7 and T1 25–75% were close to being significantly different (P=0.0503 and 0.0560, respectively).

Table 1 Patient data (mean (SD or range) or number)

	Desflurane	Isoflurane
Potency estimation		
n	24	24
Age (yr)	33 (20–60)	34 (18–51)
Weight (kg)	68 (8.3)	68 (6.6)
Height (cm)	170 (9.4)	168 (5.5)
Sex (M/F)	13/11	12/12
Onset and duration of action		
n	10	10
Age (yr)	33 (21–55)	32 (20–52)
Weight (kg)	67 (14.3)	68 (12.8)
Height (cm)	165 (9.1)	166 (8.7)
Sex (M/F)	6/4	7/3

Table 2 Maximum block attained with different doses of rocuronium (mean (SD))

Rocuronium (µg kg^{-1})	Desflurane	Isoflurane
75	14 (9.0)	25 (15.1)
150	61 (9.2)	47 (22.5)
225	75 (26.5)	80 (8.6)
300	97 (1.5)	99 (1.5)

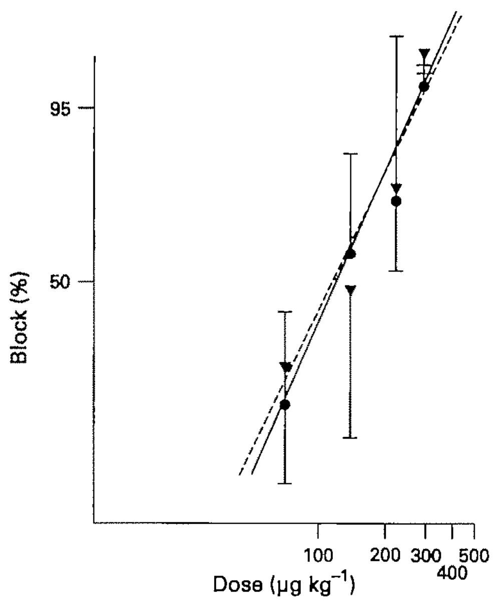

Figure 1 Dose–responses for rocuronium during anaesthesia with 1 MAC of desflurane (▲) and 1 MAC of isoflurane (●). Individual points represent mean (SD).

Table 3 ED_{50} and ED_{95} values (95% confidence intervals) for rocuronium during desflurane and isoflurane anaesthesia

	Desflurane	Isoflurane
ED_{50} (µg kg^{-1})	138 (117-162)	126 (105-151)
ED_{95} (µg kg^{-1})	281 (241-328)	283 (236-339)

Discussion

We found no significant difference in the apparent potency of rocuronium during anaesthesia with 1 MAC of desflurane or isoflurane. There are no previous reports of potency estimation of rocuronium during desflurane anaesthesia but the ED_{95} of

Table 4 Time (min) to onset and duration of block after rocuronium 0.6 mg kg^{-1} during desflurane or isoflurane anaesthesia (mean (SD))

	Desflurane	Isoflurane	*P*
Time to maximum block	1.0 (0.1)	1.1 (0.15)	0.0964
Time to recovery of			
T1 to 25%	36 (8.3)	31 (8.2)	0.1921
T1 to 90%	54 (15.4)	45 (12.7)	0.1710
TOF ratio of 0.7	66 (13.4)	52 (16.3)	0.0503
Recovery index	14 (5.3)	10 (3.2)	0.0560

rocuronium during isoflurane anaesthesia in this study was similar to that reported by previous workers[12–14] and was only marginally lower than values obtained during nitrous oxide–opioid anaesthesia[15 16].

Onset times after rocuronium 600 µg kg^{-1} were similar in both groups. These were consistent with previously published results in the absence of volatile anaesthetics using the TOF mode of stimulation[3 17] but were faster than the time of 89 s reported by Cooper and colleagues using the single twitch (at 0.1 Hz) mode of stimulation[18]. As volatile agents need to diffuse into the muscle compartments and as penetration is slow, they are unlikely to influence the onset of action of neuromuscular blockers. Our patients were exposed to the inhalation agents for 10 min before administration of rocuronium and during this time tissue concentrations would be much lower than the end-tidal concentration and therefore unlikely to affect onset of action (see below). The more likely reason for similar onset times with or without volatile anaesthetics may be the use of the TOF mode of stimulation. It has been shown previously that onset time for intermediate duration neuromuscular blocking drugs is faster using a TOF mode of stimulation[18–20].

The clinical duration of action and recovery index of rocuronium during isoflurane–nitrous oxide anaesthesia were consistent with other published studies[14 15]. Recovery times to all end-points (including recovery index) were longer with desflurane although only the times to a TOF ratio of 0.7 and the recovery index were close to being significantly different. Volatile agents require approximately 30–45 min to equilibrate between alveolar, blood and muscle compartments and are therefore less likely to affect the onset of block. This was demonstrated in the study of Cannon and colleagues who showed that it took approximately 45 min to attain steady state block after infusion of vecuronium, even with the use of volatile anaesthetics[21]. It is likely therefore that the principal effects are on recovery of block. The blood–muscle partition coefficient of desflurane is 2.02 compared with 2.92 for isoflurane[22]. Therefore, equilibration between muscle and end-tidal concentration may have been more complete for desflurane than for isoflurane. This might have increased the comparative differences between the muscle partial pressures of anaesthetic and accounted for the increased duration of action and recovery index seen in the desflurane group. Desflurane has also been postulated to have a depressant effect at the neuromuscular junction both pre- and post-junctionally[4]. The duration of action of rocuronium during desflurane anaesthesia may therefore be longer than during isoflurane anaesthesia. This was an exploratory study based on the hypothesis that there would be no difference between the groups and a larger study may show significant differences in the duration of action of rocuronium during anaesthesia with desflurane and isoflurane.

The results of this study differed from previous results with atracurium and mivacurium which showed little difference between desflurane and isoflurane[5 23]. The difference may be because of the unique metabolic pathways of these two latter blockers. In contrast, others have shown that 1 MAC of desflurane and isoflurane had a similar effect on the neuromuscular effects of vecuronium[6]. However, they used a Datex Relaxograph to monitor neuromuscular block. This instrument is known to yield somewhat different results from those obtained using mechanomyography, as used in this study[24]. In addition, these authors measured recovery to only 25% of control values. However, our results are in agreement with those of Wright and colleagues who observed that desflurane produced greater potentiation of the effects of vecuronium compared with isoflurane[25].

In summary, this study has demonstrated no difference in the estimated potency of rocuronium during anaesthesia with 1 MAC of desflurane or isoflurane. The effects of rocuronium 0.6 mg kg^{-1} were, however, longer during anaesthesia with desflurane.

References

1. Eger EI II. Partition coefficients of I-653 in human blood, saline and olive oil. *Anesthesia and Analgesia* 1987; **66**: 971–973.
2. Mirakhur RK. Newer neuromuscular blocking drugs: An overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; 44: 182–199.
3. Cooper RA, Mirakhur RK, Maddineni VR. Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anaesthesia. *Anaesthesia* 1993; **48**: 103–105.
4. Caldwell JE, Laster MJ, Magorian T, Heier T, Yasuda N, Lynam P, Eger EI, Weiskopf RB. The neuromuscular effects of desflurane, alone and combined with pancuronium or succinylcholine in humans. *Anesthesiology* 1991; **74**: 412–418.
5. Lee C, Tsai S-K, Kwan W-F, Chen ML. Desflurane potentiates atracurium in humans: a comparative study with isoflurane. *Journal of Clinical Anesthesia* 1992; 4: 448–454.
6. Ghouri AF, White PF. Comparative effects of desflurane and isoflurane on vecuronium induced neuromuscular blockade. *Journal of Clinical Anesthesia* 1992; 4: 34–38.
7. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, De Jong RH, Elashoff RM. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
8. Rampil IJ, Lockhart SH, Zwass MS, Peterson N, Yasuda N, Eger EI II, Weiskopf RB, Damask MC. Clinical characteristics of desflurane in surgical patients: minimum alveolar concentration. *Anesthesiology* 1991; 74: 429–433.
9. Gibson FM, Mirakhur RK, Lavery GG, Clarke RSJ. Potency of atracurium; a comparison of single dose and cumulative dose techniques. *Anesthesiology* 1985; **62**: 657–659.
10. Gibson FM, Mirakhur RK, Clarke RSJ, Lavery GG. Comparison of cumulative and single bolus dose techniques for determining the potency of vecuronium. *British Journal of Anaesthesia* 1985; 57: 1060–1062.
11. Armitage P. *Statistical Methods in Medical Research*. Oxford: Blackwell Scientific Publications, 1971; 349–361.
12. Quill TJ, Begin M, Glass PSA, Ginsberg B, Gorback MS. Clinical responses to Org 9426 during isoflurane anesthesia. *Anesthesia and Analgesia* 1993; 72: 203–206.
13. Lambalk LM, de Wit APM, Wierda JMKH, Hennis PJ, Agoston S. Dose–response relationship and time course of action of Org 9426. *Anaesthesia* 1991; **46**: 907–911.
14. Oris B, Crul JF, Vandermeersch E, Van Aken H, Van Egmond J, Sabbe MB. Muscle paralysis by rocuronium during halothane, enflurane, isoflurane, and intravenous anesthesia. *Anesthesia and Analgesia* 1993; 77: 570–573.
15. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ohta Y. The neuromuscular effects of Org 9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; 75: 191–196.
16. Cooper RA, Mirakhur RK, Elliott P, McCarthy GJ. Estimation of the potency of Org 9426 using two different modes of nerve stimulation. *Canadian Journal of Anaesthesia* 1992; **39**: 139–142.
17. Puhringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1992; 75: 37–40.

18. Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–273.
19. Curran MJ, Donati F, Bevan DR. Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. *British Journal of Anaesthesia* 1987; **59**: 989–994.
20. Bell PF, Gibson F, Mirakhur RK, Clarke RSJ. Comparison of single twitch and train-of-four modes of stimulation for measurement of non-depolarizing neuromuscular block. *British Journal of Anaesthesia* 1988; **60**: 343P.
21. Cannon JE, Fahey MR, Castagnoli KP, Takashi F, Canfell PC, Sharma M, Miller RD. Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; **67**: 503–506.
22. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Johnson BH, Freire BA, Fassoulaki A. Kinetics of desflurane, isoflurane and halothane in humans. *Anesthesiology* 1991; **74**: 489–498.
23. Kumar N, Mirakhur RK, Symington MJ, Loan PB, Connolly FM. A comparison of the effects of isoflurane and desflurane on the neuromuscular effects of mivacurium. *Anaesthesia* 1996; **51**: 547-550.
24. Bell PF, Mirakhur RK, Stanley JC, Clarke RSJ. Comparison of the mechanical and electromyographic responses following atracurium administration during fentanyl and isoflurane anesthesia. *Anesthesia and Analgesia* 1989; **68**: S21.
25. Wright PMC, Hart P, Lau M, Brown R, Sharma ML, Gruenke L, Fisher DM. Magnitude and time course of vecuronium potentiation by desflurane versus isoflurane. *Anesthesiology* 1995; **82**: 404–411.

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Neuromuscular blocking action of suxamethonium after antagonism of vecuronium by edrophonium, pyridostigmine or neostigmine

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Summary

The reported effects of edrophonium on a subsequent dose of suxamethonium are variable and the effects of pyridostigmine have not been evaluated extensively. We have studied this interaction in patients anaesthetized with propofol and sufentanil. After recovery from an initial bolus (1 mg kg^{-1}) of suxamethonium, vecuronium was infused to produce 75% block. After 30 min, the infusion was discontinued and saline 5 ml, edrophonium 0.75 mg kg^{-1}, pyridostigmine 0.24 mg kg^{-1} or neostigmine 0.05 mg kg^{-1} was given. Fifteen minutes later the mean durations of a second bolus of suxamethonium were: 10.5 (SD 3.9) min (saline), 10.9 (3.7) min (edrophonium), 18.7 (5.4) min (pyridostigmine) and 23.8 (7.4) min (neostigmine). Corresponding plasma cholinesterase activities (percentage of baseline) were: 91 (18), 87 (9), 21 (10) and 52 (26). When both treatment groups and individual patients were compared, the changes in duration of action did not correlate with changes in cholinesterase activity. These data suggest that other mechanisms in addition to cholinesterase inhibition may contribute to this drug interaction. (*Br. J. Anaesth.* 1996;**77**:492–495)

Key words

Neuromuscular block, suxamethonium. Antagonists neuromuscular block, edrophonium. Antagonists neuromuscular block, neostigmine. Antagonists neuromuscular block, pyridostigmine. Enzymes, cholinesterase.

At the end of a surgical procedure there is occasional need for urgent short-term neuromuscular block to retrieve a misplaced gauze sponge or relieve severe laryngospasm. Suxamethonium may be used because of its rapid onset and short duration of action. However, prior administration of a cholinesterase inhibitor to antagonize non-depolarizing neuromuscular block may prolong the duration of a subsequent dose of suxamethonium[1]. This interaction has been demonstrated consistently with pyridostigmine and neostigmine[2 3], but studies with edrophonium have produced variable results ranging from no prolongation[4] to slight prolongation[5] or increases comparable with those produced by pyridostigmine and neostigmine[6].

Because of these inconsistencies, and the absence of a single study comparing edrophonium, pyridostigmine and neostigmine in humans, we have investigated the interactions between suxamethonium and each of these cholinesterase inhibitors in patients anaesthetized for elective surgery.

Patients and methods

After obtaining approval from our Human Subjects Review Committee, written informed consent was obtained from patients undergoing elective operations with an anticipated duration of more than 3 h. Patients were excluded if they had any known neuromuscular disease, had experienced prolonged immobilization or bed rest, or were receiving any medications known to interfere with neuromuscular function. Patients were premedicated with midazolam (up to 0.03 mg kg^{-1}) i.v. Standard intraoperative monitors were attached, an antecubital vein was cannulated, a blood sample obtained for measurement of baseline plasma cholinesterase activity, surface stimulating electrodes placed over the ulnar nerve at the wrist, and the forearm fixed securely in a mechanomyogram holder. The thumb was attached to a force transducer (Model FT-10, Grass Instruments, West Warwick, RI, USA) and the resting tension adjusted to approximately 200 *g*. After preoxygenation, general anaesthesia was induced with propofol 1.0–2.5 mg kg^{-1} and sufentanil 0.25–1.0 μg kg^{-1}. The lungs were ventilated with oxygen or an oxygen–air mixture and general anaesthesia was maintained with infusions of propofol 50–250 μg kg^{-1} min^{-1} and sufentanil 0.004–0.025 μg kg^{-1} min^{-1}, adjusted as indicated clinically.

Neuromuscular function was assessed using a stimulator (Model S48, Grass Instruments) triggering a battery-operated nerve stimulator (Digi Stim II, Neuro Technology, Houston, TX, USA) and a computer-assisted data acquisition and analysis system written in the Asyst programming language. The ulnar nerve was stimulated every 2 s (single pulse, 0.1 ms duration, delivered current 60–75 mA). The analogue signal from the transducer was amplified (Model C-150 DC amplifier, Astro-Med, Inc., West Warwick, RI, USA) and digitized (100 points at 333 Hz) using an analogue-to-digital conversion board (Model 2801, Data Translations, Inc., Marlboro, MA, USA). Resting tension and peak contractile tension were calculated online. Each twitch, and

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the trend in peak tension over time, were displayed on the computer monitor.

After induction of anaesthesia, manual, controlled ventilation was continued for approximately 10 min to allow stabilization of the contractile response. Suxamethonium 1.0 mg kg^{-1} in normal saline 10 ml was infused into the hub of the antecubital catheter at a rate of 1 ml s^{-1} with the carrier solution flowing at 250 ml h^{-1}. After the onset of complete neuromuscular block, the trachea was intubated. After complete recovery from suxamethonium, as demonstrated by stable contractile tension for at least 5 min, a loading dose of vecuronium was given followed by an infusion titrated to maintain approximately 75% neuromuscular block. Thirty minutes after the loading dose of vecuronium, the infusion was discontinued and glycopyrronium 7 µg kg^{-1} was administered. Thirty seconds later, patients received a 5-ml i.v. injection containing saline, edrophonium 0.75 mg kg^{-1}, pyridostigmine 0.24 mg kg^{-1} or neostigmine 0.05 mg kg^{-1}. Fifteen minutes later, a second blood sample was obtained for measurement of serum cholinesterase activity and a second bolus of suxamethonium 1.0 mg kg^{-1} in 10 ml was injected, as described previously. A fifth group of patients also received edrophonium 0.75 mg kg^{-1}, but blood sampling and administration of suxamethonium occurred after 5 instead of 15 min.

For each suxamethonium bolus, onset time (start of injection to maximum block), recovery index (time for recovery from 25% to 75% of the final maximal twitch) and duration (start of injection to return to 90% of the final twitch) were determined.

Blood samples were centrifuged after collection. Serum was aspirated and stored at −70 °C for subsequent analysis. Serum cholinesterase activity was measured by a modification of the assay described originally by Ellman and colleagues[7] (Physicians Clinical Laboratory, Inc., Sacramento, CA, USA).

Comparisons of patient characteristics or baseline neuromuscular data were made using either the Kruskal–Wallis test (non-parametric data) or the Student–Neuman–Keul's test (parametric data). Analysis of the response to suxamethonium was made with either a paired *t* test for within-group comparisons or Dunnett's test, using saline treatment as the control response for comparisons between groups. In all cases, $P \leq 0.05$ was considered statistically significant. All values are expressed as mean (SD).

Results

We studied 50 patients (28 females, 22 males), mean age 51 (range 22 to 79) yr, mean weight 75 (2.6) kg. Eight patients were ASA I, 27 ASA II and 15 ASA III. Patients were assigned sequentially to one of five treatment groups: saline, edrophonium (5 min), edrophonium, pyridostigmine or neostigmine. There were no differences between the 10 patients in each group in terms of sex, age, weight or ASA classification.

The mean initial contractile response was 574 (91) g and was stable throughout the study. The final contractile response was 101 (16) % of the initial twitch height. The first bolus of suxamethonium had a mean onset time of 59 (15) s, duration of 13.7 (4.2) min and a recovery index of 2.6 (1.3) min. Infusion of vecuronium decreased the contractile response to 26 (7) % of the initial baseline response and required a mean total dose of 2.8 (1.0) mg. There were no differences between the groups in initial contractile response, onset, duration or recovery index for the first bolus of suxamethonium (table 1). Neuromuscular block produced by vecuronium was comparable in all groups with the exception of the edrophonium (5 min) group (80 (6) % *vs* 70 (6) % for the saline group). Correspondingly, the total dose of vecuronium administered to this group was higher (3.1 (1.1) mg *vs* 2.6 (1.6) mg).

The effects of treatment on the response to the second dose of suxamethonium are summarized in table 1. Onset time increased in all five groups (range 131–196% of control onset times). Duration of action was shorter in patients who received saline or edrophonium and prolonged in patients who received pyridostigmine (35% increase) or neostigmine (78% increase). The effects of neostigmine were significantly greater than those of pyridostigmine. Recovery index followed a similar pattern, with slightly shorter times in patients who received saline or edrophonium and prolonged times in patients who received pyridostigmine or neostigmine.

Table 1 Effects of treatment with an acetylcholinesterase inhibitor on the response to suxamethonium and plasma cholinesterase activity (mean (SD)). *Significantly different from values before treatment (paired *t* test); †Significantly different from saline group (Dunnett's test)

	Treatment				
	Saline	Edrophonium (5 min)	Edrophonium	Pyridostigmine	Neostigmine
Onset time (s)					
Before	63 (17.7)	60 (16.4)	59 (12.3)	56 (13.7)	55 (13.1)
After	97 (31.5)*	111 (21.1)*	77 (18.7)*	79 (21.3)*	99 (27.1)*
Duration of action (min)					
Before	13.9 (3.6)	12.9 (3.4)	13.4 (4.0)	13.9 (2.6)	14.6 (6.9)
After	10.5 (3.9)*	11.2 (3.5)*	10.9 (3.7)*	18.7 (5.4)*†	23.8 (7.4)*†
Recovery index (min)					
Before	2.4 (0.9)	2.2 (0.7)	2.7 (0.8)	2.6 (0.7)	3.0 (2.5)
After	1.9 (0.5)	2.1 (0.6)	2.1 (0.6)*	3.3 (1.5)	3.5 (1.2)†
Plasma cholinesterase (iu litre^{-1})					
Before	2804 (1094)	2926 (1025)	3319 (1066)	2628 (1034)	3446 (1066)
After	2442 (756)	2203 (964)*	2983 (964)*	508 (209)*†	1977 (1401)*†

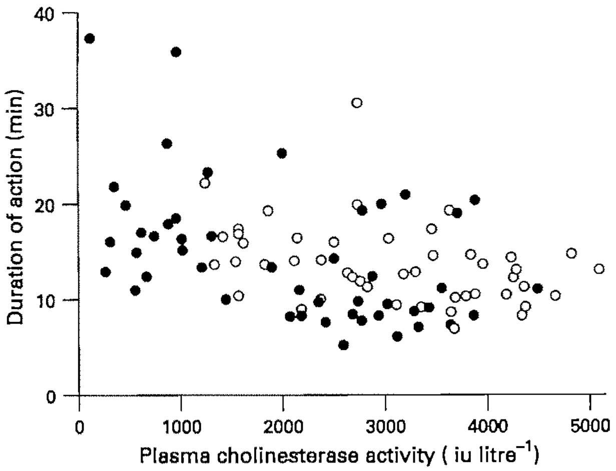

Figure 1 Relationship between plasma cholinesterase activity and duration of action produced by suxamethonium (all groups combined). Data points are for before (○) and after (●) drug treatment.

Baseline plasma cholinesterase activity ranged from 1229 to 5007 iu litre^{-1} (normal range 1000–3500 iu litre^{-1}). These values were comparable between treatment groups (table 1, fig. 1). Lower pre-drug cholinesterase activity correlated with a longer duration of action of suxamethonium. This relationship was best described by an exponential curve, consistent with previous reports[8]. Cholinesterase activity was not significantly altered by saline administration, but decreased after drug treatment in the other four groups. Post-treatment measurements were 93–4461 iu litre^{-1}. Statistically significant decreases in activity occurred after treatment with cholinesterase inhibitors but the magnitude varied widely; edrophonium (5 min) −26 (17) %; edrophonium −13 (8) %; pyridostigmine −79 (10) %; neostigmine −48 (26) %. The changes after pyridostigmine and neostigmine differed significantly from the saline control group (−9 (18) %) and from each other.

Discussion

Based on previous case reports and theoretical concerns, Sunew and Hicks studied the effects of pyridostigmine and neostigmine on the duration of subsequently administered suxamethonium[2]. Both drugs prolonged the duration of neuromuscular block. Pyridostigmine increased the mean duration of a 1-mg kg^{-1} dose to 24 min (182% of baseline) while neostigmine increased the duration to 35 min (315% of baseline). Our data confirmed this interaction. Both cholinesterase inhibitors prolonged the duration of action, and the effects of neostigmine (178% of baseline) were greater than those of pyridostigmine (135% of baseline). The smaller increases reported here probably resulted from the greater time between anticholinesterase and suxamethonium administration (15 min *vs* 5 min) and the effects of residual vecuronium on nicotinic cholinergic receptors.

Interactions between edrophonium and suxamethonium have also been evaluated previously. Mirakhur examined the effects of edrophonium on plasma cholinesterase activity in 15 patients[9]. From the lack of inhibition he inferred that edrophonium would be unlikely to prolong the effects of suxamethonium and subsequently confirmed this in patients undergoing elective surgical procedures with halothane–nitrous oxide–oxygen general anaesthesia[4]. In contrast, Sohn, Cronnelly and Sharma examined the interactions between suxamethonium and edrophonium in six surgical patients and demonstrated a transient decrease in plasma cholinesterase activity and a 60% increase in the duration of action of suxamethonium[5]. These patients also received general anaesthesia with halothane–nitrous oxide–oxygen but pancuronium, which is a significant plasma cholinesterase inhibitor[10], was used as a maintenance neuromuscular blocking agent. Patients in our study received propofol–sufentanil–oxygen as a maintenance anaesthetic which does not potentiate the actions of neuromuscular blocking drugs, and vecuronium, which does not inhibit plasma cholinesterase to any clinically significant extent[10], was used for maintenance of neuromuscular block. Our results are comparable with those of Mirakhur who demonstrated that prior treatment with edrophonium did not increase the duration of subsequently administered suxamethonium[9].

Our previous evaluation of the interactions between cholinesterase inhibitors and suxamethonium used a rat model to limit confounding variables such as volatile anaesthetic gases and anaesthetic adjuncts which inhibit plasma cholinesterase activity[6]. These studies demonstrated that all three inhibitors produced a similar (27–38%) increase in the duration of suxamethonium. However, caution is warranted when extrapolating these animal data directly to clinical practice. Studies in isolated rat muscle tissues or whole animals are used frequently to predict responses in humans, but there are quantitative differences between species[11]. Drug interactions involving metabolism by plasma cholinesterase and inhibition by anticholinesterases increase sources of variability. There are differences with regard to enzyme form and concentrations between species[12]. However, the sensitivities of the acetylcholinesterase and butyrylcholinesterase enzymes to inhibitors are similar in humans and rats[13 14]. If the pharmacokinetics and pharmacodynamics of both neuromuscular blocking agents and reversal agents were characterized fully in both species and drug administration procedures adjusted accordingly, responses in the rat model might more directly predict responses in humans. Ultimately, confirmation in a clinical setting is still required, as emphasized by the contrast between the results reported here and previous animal studies[6].

By concurrently measuring the effect of each cholinesterase inhibitor on both enzyme activity and suxamethonium duration, these studies suggest that the increased duration of action is not solely the result of inhibition of plasma cholinesterase. Edrophonium has either no inhibition[9], or a minimal, transient effect on plasma cholinesterase[5]. Neostigmine and pyridostigmine produce similar maximal inhibitory responses, but the effects of pyridostigmine are slightly prolonged[15 16]. Measurements of plasma cholinesterase activity in this study (15 min after drug administration) were consistent with this pattern of slower recovery from pyridostigmine. In contrast, neostigmine has a significantly greater effect on suxamethonium duration. Cholinesterase inhibitors have many non-cholinergic mediated actions[1]. The lack of correlation between enzyme inhibition and prolongation of suxamethonium block suggests that these or other mechanisms may also need to be considered when evaluating this drug interaction.

Both practical and theoretical conclusions can be drawn from these studies. It is not possible to know in advance which patients may require urgent paralysis after they have received a cholinesterase inhibitor. However, if suxamethonium is required, even a dose of 1 mg kg^{-1} will not have a prohibitively long duration of action, particularly if edrophonium is the reversal agent. This is true even if edrophonium is given only 5 min earlier. In the event of an extremely long duration of paralysis (>45 min) after suxamethonium, other contributing factors such as decreased plasma cholinesterase activity, atypical plasma enzyme or additional drug interactions should be considered. In addition, with the introduction of other anaesthetic adjuncts dependent on plasma cholinesterase for metabolism, such as esmolol, mivacurium and remifentanil, studies of interactions with the commonly used cholinesterase inhibitors must consider the potential for both cholinergic and non-cholinergic mediated interactions. A current example of this is the potential for a paradoxical response when a cholinesterase inhibitor is used to antagonize mivacurium neuromuscular block[17]. A similar evaluation of this drug interaction might be revealing.

Acknowledgments

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References

1. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology* 1992; 77: 785–805.
2. Sunew KY, Hicks RG. Effects of neostigmine and pyridostigmine on duration of succinylcholine action and pseudocholinesterase activity. *Anesthesiology* 1978; **49**: 188–191.
3. Bishop MJ, Hornbein TF. Prolonged effect of succinylcholine after neostigmine and pyridostigmine administration in patients with renal failure. *Anesthesiology* 1983; 58: 384–386.
4. McCoy EP, Mirakhur RK. Comparison of the effects of neostigmine and edrophonium on the duration of action of suxamethonium. *Acta Anaesthesiologica Scandinavica* 1995; 39: 744–747.
5. Sohn YJ, Cronnelly R, Sharma M. Is the duration of action of succinylcholine prolonged following antagonism of neuromuscular blockade by edrophonium? *Anesthesiology* 1984; 61: A302.
6. Valdrighi JB, Fleming NW, Smith BK, Baker GL, White DA. Effects of cholinesterase inhibitors on the neuromuscular blocking action of suxamethonium. *British Journal of Anaesthesia* 1994; 72: 237–239.
7. Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochemical Pharmacology* 1961; 7: 88–95.
8. Viby–Mogensen J. Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with genotypically normal enzyme. *Anesthesiology* 1980; **53**: 517–520.
9. Mirakhur RK. Edrophonium and plasma cholinesterase activity. *Canadian Journal of Anaesthesia* 1986; 33: 588–590.
10. Bowman WC. *Pharmacology of Neuromuscular Function*, 2nd Edn. London: Wright, 1990; 179–180.
11. Hoppe JO. Observations on the potency of neuromuscular blocking agents with particular reference to succinylcholine. *Anesthesiology* 1955; **16**: 91–124.
12. Willis JH. The measurement and significance of changes in the cholinesterase activities of erythrocytes and plasma in man and animals. *Critical Reviews in Toxicology* 1972; **1**: 153–202.
13. Ecobichon DJ, Comean AM. Pseudocholinesterases of mammalian plasma: physicochemical properties and organophosphate inhibition in eleven species. *Toxicology and Applied Pharmacology* 1973; **24**: 92–100.
14. Rao PS, Roberts GH, Pope CN, Ferguson PW. Comparative inhibition of rodent and human erythrocyte acetylcholinesterase by carbofuran and carbaryl. *Pesticide Biochemistry and Physiology* 1994; **48**: 79–84.
15. Baraka A, Wakid N, Mansour R, Haddad W. Effect of neostigmine and pyridostigmine on the plasma cholinesterase activity. *British Journal of Anaesthesia* 1981; 53: 849–851.
16. Mirakhur RK, Lavery TD, Briggs LP, Clarke RSJ. Effects of neostigmine and pyridostigmine on serum cholinesterase activity. *Canadian Journal of Anaesthesia* 1982; **29**: 55–58.
17. Naquib M, Selim M, Bakhamees H, Samarkandi AH, Turkistani A. Enzymatic versus pharmacologic antagonism of profound mivacurium-induced neuromuscular blockade. *Anesthesiology* 1996; **84**: 1051–1059.

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Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium?

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Summary

To test if recovery of neuromuscular transmission is complete after the use of neostigmine under standardized conditions, we have measured adductor pollicis mechanical activity in response to 0.1 Hz (twitch height), train-of-four (TOF) and 100 Hz (RF 100 Hz) ulnar nerve stimulations. We studied 56 adult anaesthetized (thiopentone, fentanyl, nitrous oxide in oxygen) patients, allocated randomly to one of four groups (n=14) to receive rocuronium (group Roc), vecuronium (group Vec), atracurium (group Atr) or pancuronium (group Pan). Recovery of neuromuscular transmission was studied for 15 min after neostigmine 40 μg kg^{-1} was given at 25% recovery of twitch height. Fifteen minutes after antagonism, the TOF ratio was 0.91 (SEM 0.01), 0.88 (0.02) and 0.92 (0.01) (ns), and RF 100 Hz was 0.78 (0.01), 0.79 (0.02) and 0.78 (0.01) (ns) respectively, in patients in groups Roc, Vec and Atr, respectively. In patients in group Pan, TOF ratio and RF 100 Hz were only 0.76 (0.01) and 0.33 (0.04) respectively (P<0.01, one-way analysis of variance, Duncan's multiple classification range tests). In contrast with pancuronium, antagonism of rocuronium-, vecuronium- and atracurium-induced neuromuscular blocks produced a similar high degree of recovery of neuromuscular transmission. (*Br. J. Anaesth.* 1996;**77**:496–499)

Key words

Neuromuscular block, rocuronium. Neuromuscular block, vecuronium. Neuromuscular block, atracurium. Neuromuscular block, pancuronium. Antagonists neuromuscular block, neostigmine. Measurement techniques, neuromuscular block. Neuromuscular block, measurement of response.

Recently, Eriksson and colleagues showed in awake volunteers receiving vecuronium to stabilize the TOF ratio at 0.7, that while the ventilatory response to hypercapnia was normal, reflex hyperventilation induced by hypoxaemia was depressed. This test returned to normal when the TOF ratio returned to 0.9[1 2]. These observations cast doubt on the often proposed 0.7 TOF ratio as a "gold standard" to guarantee a safe clinical situation and also raised interest in the 0.9 TOF ratio as a new end-point for defining adequate recovery of neuromuscular transmission.

In normal patients receiving medium duration neuromuscular blocking agents (rocuronium[3–7], vecuronium, atracurium) a TOF ratio of 0.7 is currently obtained after administration of neostigmine given at a twitch height of 10–25%, but even for vecuronium, data related to a TOF ratio of 0.9 are still scarce[8–12].

In addition to the 2 Hz TOF stimulation pattern, the use of high stimulation rates, especially 100 Hz tetanic stimulation, to quantify recovery of neuromuscular transmission may be desirable because of the TOF ratio limitations for detection of residual neuromuscular block in many clinical situations[8–12]. In normal awake patients also, firing rates of approximately 100 Hz are often observed in different muscle types[13].

The purpose of this study was to assess the level of recovery of neuromuscular transmission 15 min after administration of neostigmine 40 μg kg^{-1} with atropine 15 μg kg^{-1} in patients receiving rocuronium, vecuronium, atracurium and pancuronium.

Patients and methods

After obtaining approval from the hospital Ethics Committee for Human Research and written informed consent, we studied 56 young, healthy adult patients, ASA I and II, undergoing elective lower limb surgery. None had clinical or routine biochemical evidence of hepatic or renal damage. All were devoid of neuromuscular disease and drugs that are known to interfere with neuromuscular transmission.

Patients received lormetazepam 0.2 mg kg^{-1} orally, 1 h before anaesthesia, which was induced with thiopentone 3–5 mg kg^{-1} i.v. After loss of consciousness, ventilation was controlled manually (with 50% nitrous oxide in oxygen). The trachea was intubated after i.v. administration of one of the four neuromuscular blockers. Thereafter, ventilation was controlled mechanically (open circuit, 65% nitrous oxide in oxygen) and adjusted to produce an end-tidal carbon dioxide partial pressure of 4.4 (0.3) kPa. For maintenance of anaesthesia, patients received fentanyl 5 μg

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kg^{-1} and dehydrobenzperidol 100 μg kg^{-1} i.v., followed by bolus doses of fentanyl 2 μg kg^{-1} if there was clinical evidence of inadequate analgesia. Heat loss from the body surface and the arms was controlled by the use of a water warming mattress (autoregulation on 37 °C rectal temperature) and surgical sheets (monitored hypothenar temperature greater than 35 °C).

To measure isometric contraction of the adductor pollicis, a force displacement transducer (UC3 cell Statham TM), fitted with tension attenuator (ULE-20, Statham TM) and incorporated in a hand grip, was preloaded to 100 *g* and secured with adhesive tape onto the patient's left hand. Mechanical activity of the adductor pollicis was induced by square wave pulses of 0.2 ms duration at supramaximal intensity, delivered at 0.1 Hz from an Organon Teknika Digit-Stim III TM stimulator, via two paediatric surface electrodes placed near the ulnar nerve at the wrist. The resulting analogue signals were amplified and recorded. Skin thenar temperature was measured with a surface electrothermometer (YSI 409B TM).

The 56 patients were allocated randomly to one of four groups of 14 patients each to receive rocuronium (group Roc), vecuronium (group Vec), atracurium (group Atr) or pancuronium (group Pan). After a 5-min recording of control twitch height, 100 Hz, 5-s duration was assessed and control RF 100 Hz was measured during thiopentone–fentanyl–nitrous oxide in oxygen anaesthesia, but in the absence of neuromuscular blocker. When twitch height had regained its control value, rocuronium 600 μg kg^{-1}, vecuronium 100 μg kg^{-1}, atracurium 500 μg kg^{-1} or pancuronium 80 μg kg^{-1} was given i.v. Thereafter, to achieve a neuromuscular block of about 1 h, when twitch height had spontaneously regained 25% of control, patients received two additional doses of rocuronium 120 μg kg^{-1} (group Roc), vecuronium 20 μg kg^{-1} (group Vec), atracurium 100 μg kg^{-1} (group Atr), while in group Pan, patients received only an initial dose of pancuronium 80 μg kg^{-1}.

The 56 randomized patients received atropine 15 μg kg^{-1} mixed with neostigmine 40 μg kg^{-1} at the end of the surgical procedure, exactly when twitch height had spontaneously regained 25% of control. Thereafter, twitch height (every 10 s) and TOF ratio (2 Hz, every 3 min) were measured for 15 min in the four groups. Immediately after the TOF ratio at 15 min, 100 Hz tetanic stimulation, 5-s duration, was assessed. Residual force after 100 Hz tetanic stimulation (RF 100 Hz) was calculated as the ratio between tension at the end of the 5-s stimulation period and maximum response registered. Statistical analysis of the data was performed using one-way analysis of variance[14]. In case of significant differences observed by ANOVA, Duncan's multiple classification range tests were performed to indicate the best recovery scores.

Table 1 Patients characteristics (mean (SEM) [range]). Clinical duration of block = time elapsed from maximum block achieved after the initial dose of neuromuscular blocker to administration of neostigmine

Group	Age (yr)	Weight (kg)	Height (cm)	Clinical duration of block (min)
Roc	38 [20–56]	75 (3)	176 (2)	68 (5) [43–86]
Vec	39 [18–58]	70 (3)	170 (2)	67 (6) [42–96]
Atr	35 [18–57]	76 (4)	174 (2)	70 (6) [44–100]
Pan	37 [27–47]	73 (3)	174 (3)	68 (5) [45–130]

Results

There were no significant differences between patients in the four groups in terms of their characteristics (table 1). Mean age of all patients was 37 (range 18–58) yr, mean weight 73 (SEM 2) (53–108) kg and mean height 174 (1) (154–194) cm (n=56) (table 1). Mean clinical duration of neuromuscular block (time elapsed from maximum block achieved after the initial dose of neuromuscular blocker to administration of neostigmine) was 69 (SEM 3) min for all patients (n=56), and 68 (5) (range 43–86) min, 67 (6) (42–96) min, 70 (6) (44–100) min and 68 (6) (45–130) min in patients in groups Roc, Vec, Atr and Pan, respectively (table 1). Control RF 100 Hz during thiopentone–nitrous oxide in oxygen anaesthesia under normothermal conditions (cutaneous hypothenar temperature greater than 35 °C), but in the absence of neuromuscular blockers, was 0.9 (0.003) (0.85–0.95) (n=56).

At the time of antagonism, when twitch height had regained 25% of its control value, mean TOF ratio was 0.07 (0.003) for all patients (range 0.02–0.14) and there were no significant differences between the four groups (fig. 1). Evolution of the TOF ratios were similar in patients who received rocuronium 840 μg kg^{-1}, vecuronium 140 μg kg^{-1} and atracurium 700 μg kg^{-1}, except that the TOF ratio was significantly higher (0.68 (0.03); $P<0.05$) 3 min after neostigmine 40 μg kg^{-1} in patients who received vecuronium compared with those who received rocuronium (0.57 (0.03)) and atracurium (0.56 (0.03)). Fifteen minutes after administration of neostigmine, TOF ratios were 0.91 (0.01) (range 0.81–0.95), 0.88 (0.02) (0.71–0.99) and 0.92 (0.01) (0.87–0.95) in groups Roc, Vec and Atr, respectively (fig. 1). In con-

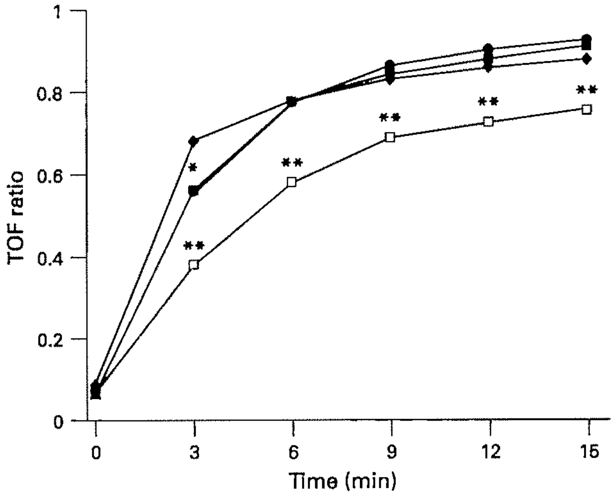

Figure 1 Evolution of the train-of-four (TOF) ratio (mean) recorded at 3-min intervals after administration of neostigmine 40 μg kg^{-1} when twitch height had returned to 25% of its initial value in groups Roc (■), Vec (♦), Atr (●) and Pan (□). *$P<0.05$, one-way analysis of variance and Duncan multiple classification range tests (group Vec *vs* groups Roc and Atr). **$P<0.01$, one-way analysis of variance and Duncan multiple classification range tests (group Pan *vs* groups Vec, Roc, Atr).

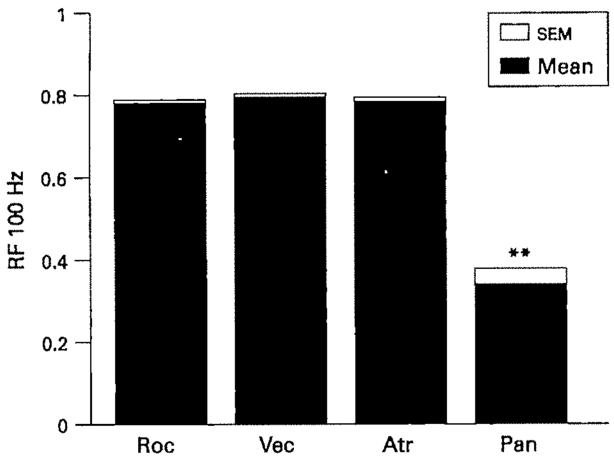

Figure 2 Values for residual force (RF) after 100 Hz tetanic stimulation (RF 100 Hz) recorded 15 min after administration of neostigmine 40 μg kg^{-1} when twitch height had regained 25% of its initial value (mean, SEM). **$P<0.01$, one-way analysis of variance, Duncan multiple classification range tests (group Pan *vs* groups Roc, Vec and Atr).

trast, during the 15-min period after administration of atropine–neostigmine, TOF ratios were always lower ($P<0.01$) in patients who received pancuronium 80 μg kg^{-1} (fig. 1). At 15 min, the TOF ratio was 0.76 (0.01) (0.67–0.86) (fig.1). Fifteen minutes after administration of neostigmine, mean values for RF 100 Hz were similar in groups Roc, Vec and Atr: 0.78 (0.01) (0.71–0.85), 0.79 (0.02) (0.60–0.95) and 0.78 (0.01) (0.65–0.85), respectively. These values were much higher ($P<0.01$) than the RF 100 Hz of 0.33 (0.04) (0.09–0.65) measured in group Pan (fig. 2).

Discussion

Our results have confirmed previous data indicating that rocuronium, in common with vecuronium and atracurium, can be antagonized easily to an end-point of a TOF ratio of 0.7 when neostigmine 40 μg kg^{-1} is given at 25% recovery of control twitch height[9-12]. But the "gold standard" of these authors (a TOF ratio of 0.7) does not imply complete recovery of neuromuscular transmission. Moreover, Eriksson and colleagues showed recently that the ventilatory response to hypoxaemia was depressed if the TOF ratio was reduced to 0.7 by vecuronium in awake volunteers, and that it returned to normal when the TOF ratio was 0.9[12]. These results suggest that a TOF ratio of 0.9 may be considered as a new end-point for defining adequate recovery of neuromuscular transmission. In patients who received rocuronium, our data indicated that such a high (0.9) TOF ratio may be observed 15 min after administration of neostigmine 40 μg kg^{-1} when twitch height has regained 25% of its initial value, in common with patients who received vecuronium and atracurium. In contrast, under the same conditions, a TOF ratio of only approximately 0.75 was observed in patients who received pancuronium.

RF 100 Hz mean values ranged from 0.8 to 0.9, associated with a TOF ratio of 0.9, and were also observed previously to antagonize vecuronium-induced block, 15 min after administration of neostigmine 40 μg kg^{-1} at 25–50% twitch height[8 9 11 12]. Mean values in patients who received rocuronium were as high (about 0.8) as in patients who received vecuronium and atracurium. In contrast with patients who received neuromuscular blockers of intermediate duration of action, the mean value for RF 100 Hz in patients in group Pan was only approximately 0.3, confirming the previously reported very high sensitivity of measured RF 100 Hz[8-12]. The use of RF 100 Hz is important also because a small, but statistically significant and clinically important 0.15 TOF ratio difference is amplified by a factor of 3–4 for the compound investigated in this study. Moreover, our data were obtained in the absence of halogenated agents, which are known to potentiate neuromuscular blockers and impair antagonism of non-depolarizing neuromuscular blockers by anticholinesterases[15-19] by various mechanisms[20 21]. In the past, the response to 100 Hz tetanic stimulation was also observed by Kopman, Epstein and Flashburg in halothane anaesthetized patients[22]. Pancuronium-induced block was antagonized when the TOF ratio was in excess of 0.1 with 5-mg increments of edrophonium until the TOF ratio exceeded 0.7. At a mean TOF ratio of 0.79, the mean value of the response to 100 Hz, 2 s tetanic stimulation, was very weak (0.28), indicating incomplete recovery of neuromuscular transmission when poor reversal conditions co-exist (long-acting neuromuscular blockers and sustained concentrations of halogenated agents).

When recovery of neuromuscular transmission was assessed by measuring the TOF ratio, neostigmine 36–50 μg kg^{-1}, given at 10% twitch height, produced a mean TOF ratio of approximately 0.7–0.8 after a 20–30-min period in fentanyl–nitrous oxide in oxygen anaesthetized patients and a TOF ratio of approximately 0.6 in enflurane–or halothene–nitrous oxide in oxygen anaesthetized patients[15 23]. In contrast, in a previous study in humans, vecuronium and pancuronium were considered to be antagonized effectively and equally by neostigmine because the duration of the effect of neostigmine on twitch height recovery was not different[24]. However, when assessing recovery of neuromuscular transmission, monitoring twitch height appears to be an insensitive test. Twitch height has little or no discriminating ability for the influence of pre-reversal twitch heights or edrophonium and neostigmine dose, or both, mainly because apparent antagonism by these measures is so complete[10 11]. Whalley, Lewis and Bedocs showed also that equipotent doses of atracurium, compared with pancuronium, were not associated with a shorter time to complete recovery from neuromuscular block induced by pancuronium[25]. In this study, all patients received an initial dose of pancuronium 0.1 mg kg^{-1}; no patient received only atracurium and complete recovery was defined by a TOF ratio of 0.7.

In patients receiving short-acting neuromuscular blockers such as mivacurium, neostigmine, given under the same clinical conditions, also accelerated recovery of the TOF ratio to 0.9. However, unlike the patients in this study who received medium-acting neuromuscular blockers, all patients obtained a TOF ratio of 0.9 within 15 min of administration of neostigmine, compared with 50% of patients during spontaneous recovery of mivacurium-induced block[26]. The use of short-acting neuromuscular blockers such as mivacurium should probably make adequate or even complete antagonism an easier problem to solve in many patients.

References

1. Eriksson LI, Lennmarken C, Wyon N, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 710–715.
2. Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. *Anesthesiology* 1993; **78**: 693–699.
3. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall JG. Effects of a new neuromuscular blocking agent ORG 9426 in anaesthetized cats and pigs and in isolated nerve–muscle preparations. *British Journal of Anaesthesia* 1989; **63**: 400–410.
4. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ohta Y. The neuromuscular effects of ORG 9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; **75**: 191–196.
5. Lambalk LM, Dewit APM, Wierda JMKH, Hennis PJ, Agoston S. Dose–response relationship and time course of action of ORG 9426. *Anaesthesia* 1991; **46**: 907–911.
6. Naguib M, Abdulatif M, Al-Ghamdi A. Dose–response relationships for edrophonium and neostigmine antagonism of rocuronium bromide (ORG 9426)-induced neuromuscular blockade. *Anesthesiology* 1993; **79**: 739–745.
7. Van den Broek L, Proost JH, Wierda JMKH, Njoo MD, Hennis PJ. Neuromuscular and cardiovascular effects of neostigmine and methyl-atropine administered at different degrees of rocuronium-induced neuromuscular block. *European Journal of Anaesthesia* 1994; **11**: 481–487.
8. Baurain MJ, d'Hollander AA, Melot C, Dernovoi BS, Barvais L. Effects of residual concentrations of isoflurane on the reversal of vecuronium-induced neuromuscular blockade. *Anesthesiology* 1991; **74**: 474–478.
9. Baurain MJ, Dernovoi BS, d'Hollander AA, Barvais L. The influence of atropine dose on recovery from vecuronium-induced neuromuscular blockade. *Anesthesiology* 1992; **77**: 17–20.
10. Baurain MJ, Dernovoi BS, d'Hollander AA, Hennart DA, Cantraine FR. Low and high frequency stimulation tests to characterize the effects of edrophonium on vecuronium-induced neuromuscular block. *British Journal of Anaesthesia* 1995; **74**: 12–15.
11. Baurain MJ, Dernovoi BS, d'Hollander AA, Hennart DA, Cantraine FR. Conditions to optimise the reversal action of neostigmine upon a vecuronium-induced neuromuscular block. *Acta Anaesthesiologica Scandinavica* 1996; **40**: 574–578.
12. Baurain MJ, Hoton F, Dernovoi BS, d'Hollander AA. Influence and relative sensitivities of 50 Hz and 100 Hz tetanic stimuli on subsequent tetanic fade ratios in patients receiving vecuronium. *Anesthesia and Analgesia* 1996; **82**: 139–142.
13. Sharp JT, Hyatt RE. Mechanical and electrical properties of respiratory muscles. In: Geiger SR, Fishman AP, eds. *Handbook of Physiology, Section 3: The Respiratory System, Volume III: Mechanics of Breathing Part 2*. Baltimore: Williams & Wilkins Company, 1986; 402–403.
14. Norusis MJ. One-way analysis of variance: procedure oneway. In: Norusis MJ, ed. *SPSS/PC$^+$*. Chicago, Statistical Programs for Social Sciences, Inc., 1986; B152–B163.
15. Deslile S, Bevan DR. Impaired antagonism of pancuronium during enflurane anaesthesia in man. *British Journal of Anaesthesia* 1982; **54**: 441–445.
16. Dernovoi B, Agoston S, Barvais L, Baurain M, Lefebvre R, d'Hollander AA. Neostigmine antagonism of vecuronium paralysis during fentanyl, halothane, isoflurane and enflurane anesthesia. *Anesthesiology* 1987; **66**: 698–701.
17. Gill SS, Bevan DR, Donati F. Edrophonium antagonism of atracurium during enflurane anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 300–305.
18. Morita T, Tsukagoshi H, Sugaya T, Saito S, Sato H, Fujita T. Inadequate antagonism of vecuronium-induced neuromuscular block by neostigmine during sevoflurane or isoflurane anesthesia. *Anesthesia and Analgesia* 1995; **80**: 1175–1180.
19. Fukushima K. Interactions of volatile anesthetics with non-depolarizing neuromuscular blocking agents. In: Fukushima K, Ochiai R, eds. *Muscle Relaxants. Physiologic and Pharmacologic Aspects*. Tokyo: Springer Verlag, 1995; 269–274.
20. Brett RS, Dilger JP, Yland KF. Isoflurane causes "flickering" of the acetylcholine receptor channel: observations using the patch clamp. *Anesthesiology* 1988; **69**: 161–170.
21. Griffiths R, Greiff JM, Boyle E, Rowbotham DJ, Norman RI. Volatile anesthetic agents inhibit choline uptake into rat synaptosomes. *Anesthesiology* 1994; **81**: 953–958.
22. Kopman AF, Epstein RH, Flashburg MH. Use of 100-Hertz tetanus as an index of recovery from pancuronium-induced non-depolarizing neuromuscular blockade. *Anesthesiology* 1982; **61**: 439–441.
23. Kopman AF. Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. *Anestheriology* 1986; **65**: 572–578.
24. Gencarelli PJ, Miller RD. Antagonism of ORG NC45 (vecuronium) and pancuronium neuromuscular blockade by neostigmine. *British Journal of Anaesthesia* 1982; **54**: 53–56.
25. Whalley DG, Lewis B, Bedocs NM. Recovery of neuromuscular function after atracurium and pancuronium maintenance of pancuronium block. *Canadian Journal of Anaesthesia* 1994; **41**: 31–35.
26. Baurain MJ, Dernovoi BS, d'Hollander AA, Hennart DA. Comparison of neostigmine-induced recovery with spontaneous recovery from mivacurium-induced neuromuscular block. *British Journal of Anaesthesia* 1994; **73**: 791–794.

British Journal of Anaesthesia 1996;77:500–502

Chronic carbamazepine therapy does not influence mivacurium-induced neuromuscular block

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Summary

Patients receiving anticonvulsant drugs chronically are relatively resistant to some non-depolarizing neuromuscular blocking drugs. We investigated the influence of chronic carbamazepine therapy on neuromuscular block induced by mivacurium in 20 otherwise healthy individuals undergoing neurosurgical operations, 10 of whom were receiving chronic treatment with carbamazepine and the other 10 served as controls. The median duration of carbamazepine therapy was 22 weeks (range 4–182 weeks). After premedication with oral diazepam, anaesthesia was induced with fentanyl and thiopentone and maintained with 0.5% isoflurane and nitrous oxide in oxygen. The ulnar nerve was stimulated and the evoked electromyogram recorded using a Datex NMT monitor. Mivacurium 0.15 mg kg^{-1} ($2\times ED_{95}$) was given as a bolus i.v. Based on the response to the first of four stimuli, lag time, onset-time, times to recovery to 10%, 25%, 50% and 75% of baseline responses and recovery index (RI 25–75%) did not differ between the two groups. We conclude that mivacurium-induced neuromuscular block was not influenced by preceding chronic carbamazepine therapy. (*Br. J. Anaesth.* 1996;**77**:500–502)

Key words

Anticonvulsants. Neuromuscular block, mivacurium. Neuromuscular block, measurement of response.

Patients receiving chronic carbamazepine therapy show a relative resistance to the neuromuscular effects of vecuronium[1 2], pancuronium[3], doxacurium[4] and pipecuronium[5]. Resistance to vecuronium was manifested as an increased ED_{50}[1]. For the other neuromuscular blockers and also vecuronium, resistance was documented either by increased hourly requirements for maintenance of a constant neuromuscular block or by a shorter duration of action[2–5]. Recovery time was decreased by 65% after an i.v. bolus dose ($2\times ED_{95}$) of pancuronium[3].

Mivacurium chloride is a new short-acting non-depolarizing neuromuscular blocking agent. Enzymatic hydrolysis catalysed by plasma cholinesterase is the primary metabolic pathway and distinguishes mivacurium from all other non-depolarizing neuromuscular blockers[6 7]. The distinct degradation pathway of mivacurium stimulated us to investigate the interaction between carbamazepine and mivacurium in neurosurgical patients. A report on a similar topic appeared recently after we had concluded our experiments[8].

Patients and methods

After obtaining approval from the Institutional Ethics Committee at the University Hospital of Vienna and written informed consent, we studied 20 patients, ASA I–III, undergoing various neurosurgical procedures. All patients were free of cardiac, renal, pulmonary, hepatic and neuromuscular diseases. Individuals receiving medications thought to potentially affect neuromuscular transmission were excluded, as were those undergoing deliberate hypotension during operation. Patients with psychiatric diseases, those with a recent history of alcohol or drug abuse, and those with known or suspected reduced activity of plasma cholinesterase or with an atypical form of the enzyme were also excluded. Plasma cholinesterase was measured and found to be within the normal range in all subjects. No further characterization of the enzyme was performed. Ten patients (group I) were receiving continuous carbamazepine therapy for seizure disorders for at least 4 weeks. Plasma concentrations of carbamazepine, measured by radioimmunoassay, were determined before surgery and were within the therapeutic range (15–40 μmol $litre^{-1}$). Control patients (group II) received no anticonvulsants.

All patients were premedicated with oral diazepam 10 mg, 1 h before surgery. Anaesthesia was induced with fentanyl 3–4 μg kg^{-1} and thiopentone 4–6 mg kg^{-1}, and maintained with 0.5% inspired isoflurane and 70% nitrous oxide in oxygen, and supplementary doses of fentanyl. After tracheal intubation, the lungs were ventilated mechanically to maintain end-tidal carbon dioxide partial pressure at 4.0–4.4 kPa. Oesophageal temperature was maintained greater than 36 °C with convective heating (Bair Hugger). Routine patient monitoring included continuous ECG, invasive arterial pressure, pulse oximetry, end-tidal capnography and oesophageal temperature probe.

Neuromuscular transmission was monitored with the Datex Neuromuscular Transmission Monitor

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NMT measuring the evoked electromyographic response (EMG) of the abductor digiti minimi muscle to supramaximal stimulation of the ulnar nerve at the wrist. The NMT delivered trains-of-four supramaximal square wave impulses (100 µs width) at 2 Hz. The trains were repeated every 20 s. The heights of the EMG responses to the first stimuli in the train (as percentage of baseline) were recorded by a printer connected to the monitor. To minimize movement-induced artefacts, the patient's hand was secured carefully to a padded board and the hand kept warm. The system was calibrated for each patient after induction of anaesthesia but before administration of mivacurium. The control EMG was recorded for a 3-min period and a stable baseline was obtained in each patient. Thereafter, a bolus dose of mivacurium 0.15 mg kg^{-1} (2×ED$_{95}$) was given i.v. The time required for the first response to decrease noticeably below the control level (lag time), time to disappearance of all responses (onset time), and times for T1 to recover to 10%, 25%, 50% and 75% of baseline were measured in all patients. Recovery index (RI) was calculated as the time required for the responses to the first stimuli to recover from 25% to 75% of baseline.

Comparisons were made between the carbamazepine and control groups using the two tailed Student's *t* test for independent samples and the nominal 5% level of statistical significance. In addition, a comprehensive exploratory statistical analysis of the data was performed. A sample size of 10 patients per treatment group can be justified by the subsequent rationale: setting the nominal alpha risk (two-sided) to 5% and defining the clinically relevant difference between the means of both groups as exceeding 1.3-fold of the standard deviation, yields a power of 80% with a sample size of 10 patients per treatment group.

Results

Patient data were similar in the control and carbamazepine groups (table 1). The shortest period of carbamazepine treatment was 4 weeks, the longest 182 weeks (median 22 weeks). Daily doses ranged from 300 to 1200 mg. Mean preoperative blood concentrations of carbamazepine were 27.4 (SD 9.9) µmol litre^{-1}.

The EMG response to mivacurium in both groups is shown in table 2. The EMG response to the first stimulation in the train was decreased by at least 95% in all patients. The times required for the response to recover to baseline were not significantly different between the control patients and those receiving chronic carbamazepine therapy.

Discussion

We have demonstrated that mivacurium-induced neuromuscular block was unaffected by chronic carbamazepine therapy. Although all measured variables of recovery were slightly shorter in the carbamazepine-treated group compared with the control group, the differences were not statistically significant. We conclude that chronic treatment with carbamazepine has no effect on neuromuscular block produced by mivacurium. Similar findings were reported recently for patients receiving chronic treatment with carbamazepine and other antiepileptic drugs[8]. In this respect mivacurium differs from vecuronium, pancuronium, doxacurium and pipecuronium[2-5], as the duration of action of these drugs was diminished by more than 40% in patients treated with carbamazepine.

Table 1 Patient data (mean (SD or range) or number). No significant differences between groups

	Carbamazepine (n=10)	Control (n=10)
Age (yr)	49.9 (19–70)	41.0 (18–68)
Weight (kg)	75.8 (13.3)	70.0 (11.0)
Sex (F/M)	4/6	5/5

Table 2 Lag time, onset, recovery times and recovery index (mean (SD) min) after a bolus dose of mivacurium 0.15 mg kg^{-1} (2×ED$_{95}$). No significant differences between groups

	Carbamazepine (n=10)	Control (n=10)
Lag time	0.7 (0.3)	0.8 (0.3)
Onset	3.6 (1.2)	3.9 (1.2)
10% recovery	12.7 (6.5)	13.0 (6.7)
25% recovery	16.2 (7.3)	16.9 (7.0)
50% recovery	19.5 (7.7)	21.6 (8.6)
75% recovery	24.9 (9.3)	26.3 (9.8)
Recovery index	8.7 (3.7)	9.3 (4.0)

The reasons why carbamazepine treatment reduces the potency and duration of action of some non-depolarizing neuromuscular blockers while not influencing others is still unclear. Both pharmacokinetic and pharmacodynamic explanations have been proposed. The pharmacodynamic explanation is based on the assumption that treatment with anticonvulsants decreases the affinity of the acetylcholine receptor for neuromuscular blockers or increases the number of receptors on muscle fibres[9-11]. This explanation could account for the increased ED$_{50}$ of vecuronium[1] and, at least in part, for the shorter duration of neuromuscular block. Our study was not designed to test the potency of mivacurium in patients receiving carbamazepine therapy and, hence, the possible effect of carbamazepine on the interaction of mivacurium with receptors remains open.

The pharmacokinetic explanation for the shortened duration of action of vecuronium in patients receiving carbamazepine therapy is supported strongly by the finding of Alloul and coworkers[12]. These authors reported that systemic clearance is markedly higher in treated than in control patients. The faster elimination of vecuronium could account for the shorter duration of action. As vecuronium concentrations at the site of action required for half-maximal neuromuscular block were similar in the control and treated patients (EC$_{50}$ of 151.1 (SEM 19.2) and 125.0 (11.2) ng ml^{-1}, respectively), the authors could not substantiate the hypothesis that treatment with carbamazepine lowers the affinity of the receptors for vecuronium. Increased systemic clearance of vecuronium induced by carbamazepine may be attributed to more rapid hepatic uptake and metabolism of vecuronium. As hepatic uptake and metabolism are irrelevant for mivacurium, neither its rate of degradation nor its duration of action would be expected to be altered by treatment with carbamazepine.

The action of atracurium was also reported not to be affected by chronic anticonvulsant therapy[13-15], although there is one contradictory report[16]. We suggest that the common denominator for the different findings with mivacurium and atracurium is that their distinct degradation pathway is not influenced by carbamazepine.

Although the pharmacokinetic explanation in terms of enhanced elimination of some but not other neuromuscular blockers by carbamazepine appears plausible, pharmacodynamic mechanisms may also be involved. To elucidate these mechanisms in more detail, further pharmacokinetic, pharmacodynamic and electrophysiological studies are needed. In clinical practice, however, mivacurium may be preferred in patients receiving chronic anticonvulsant therapy when a brief but predictable duration of neuromuscular block is required or neuromuscular monitoring is unavailable.

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References

1. Whalley DG, Ebrahim ZY. Influence of carbamazepine on the dose–response relationship of vecuronium. *British Journal of Anaesthesia* 1994; 72: 125–126.
2. Norman J. Resistance to vecuronium. *Anaesthesia* 1993; 48: 1068–1069.
3. Roth S, Ebrahim ZY. Resistance to pancuronium in patients receiving carbamazepine. *Anesthesiology* 1987; 66: 691–693.
4. Ornstein E, Matteo RS, Weinstein JA, Halevy JD, Young WL, Abou-Donia MM. Accelerated recovery from doxacurium-induced neuromuscular blockade in patients receiving chronic anticonvulsant therapy. *Journal of Clinical Anesthesia* 1991; 3: 108–111.
5. Jellish WS, Modica PA, Tempelhoff R. Accelerated recovery from pipecuronium in patients treated with anticonvulsant therapy. *Journal of Clinical Anesthesia* 1993; 5: 105–108.
6. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RP, Sunder N, Weakly JN, Wasila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B 1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology* 1988; **68**: 723–732.
7. Cook RD, Freeman JA, Lai AA, Kang Y, Stiller RL, Aggarwal S, Harrelson JC, Welch RM, Samara B. Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. *British Journal of Anaesthesia* 1992; **69**: 580–585.
8. Jellish WS, Thalji Z, Brundidge PK, Tempelhoff R. Recovery from mivacuriuminduced neuromuscular blockade is not affected by anticonvulsant therapy. *Journal of Neurosurgical Anesthesiology* 1996; **8**: 4–8.
9. Benzi G, Arrigoni E, Scelsi R, Marzatico F, Gorini A, Villa RF. Acetylcholine esterase sensitivity to chronic administration of diphenylhydantoin and effects on cerebral enzymatic activities related to energy metabolism. *Neurochemical Research* 1980; 5: 905–911.
10. Kim CS, Arnold FJ, Itani MS, Martyn JAJ. Decreased sensitivity to metocurine during long-term phenytoin therapy may be attributable to protein binding and acetylcholine receptor changes. *Anesthesiology* 1992; 77: 500–506.
11. Ornstein E, Matteo RS, Young WL, Diaz J. Resistance to metocurine-induced neuromuscular blockade in patients receiving phenytoin. *Anesthesiology* 1985; **63**: 294–298.
12. Alloul K, Whalley DG, Shutway F, Ebrahim Z, Varin F. Pharmacokinetic origin of carbamazepine-induced resistance to vecuronium neuromuscular blockade in anesthetized patients. *Anesthesiology* 1996; **84**: 330–339.
13. Ornstein E, Matteo RS, Schwartz AE, Silverberg PA, Young WL, Diaz J. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; **67**: 191–196.
14. Ebrahim ZY, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium or vecuronium. *Anesthesia and Analgesia* 1988; **67**: S55.
15. Spacek A, Neiger FX, Katz RL, Watkins WD, Spiss CK. No effect of chronic carbamazepine therapy on atracurium-induced neuromuscular blockade! *Anesthesia and Analgesia* 1995; **80**: S464.
16. Tempelhoff R, Modica PA, Jellish WS, Spitznagel EL. Resistance to atracuriuminduced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesthesia and Analgesia* 1990; 71: 665–669.

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LABORATORY INVESTIGATIONS

Thiobarbiturates suppress depolarization-induced contraction of vascular smooth muscle without suppression of calcium influx

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Summary

We have studied the effects of barbiturates on vascular smooth muscle tension and cytosolic calcium concentrations ([Ca^{2+}]$_i$) in endothelium-denuded rat aortic rings, preloaded with fluo-3. Changes in [Ca^{2+}]$_i$ were estimated by the fluorescence intensity of the calcium-bound form of fluo-3. In aortic rings under basal conditions, thiobarbiturates (thiopentone and thiamylal 100–300 µmol litre^{-1}) increased [Ca^{2+}]$_i$, concomitantly with an increase in tension, although oxybarbiturates (pentobarbitone and secobarbitone up to 300 µmol litre^{-1}) had no effect. Thiopentone (300 µmol litre^{1})-induced increases in tension and fluorescence intensity were mean 25.1 (SD 3.2) % and 55.0 (6.0) %, respectively, of those induced by KCl 30 mmol litre^{-1} (n=8, each). In KCl (30 mmol litre^{-1})-precontracted aortic rings, thiopentone decreased tension without reduction of [Ca^{2+}]$_i$, whereas pentobarbitone decreased tension and [Ca^{2+}]$_i$. KCl (30 mmol litre^{-1})-induced contraction was suppressed by pretreatment with all barbiturates (100–300 µmol litre^{-1}); thiopentone 300 µmol litre^{-1} suppressed contraction to 64.8 (2.5) % (n=6) and pentobarbitone 300 µmol litre^{-1} to 57.5 (2.2) % (n=9). However, the increase in [Ca^{2+}]$_i$ was suppressed by oxybarbiturates (pentobarbitone 300 µmol litre^{-1} to 77.9 (5.2) %; n=9), but not altered by thiobarbiturates. These results suggest that thiobarbiturates and oxybarbiturates affect vascular smooth muscle differently and that the affected site in thiobarbiturate-induced vasodilatation is distal to regulation of [Ca^{2+}]$_i$. (*Br. J. Anaesth.* 1996;**77**:503–507)

Key words

Muscle vascular, responses. Anaesthetics i.v., thiopentone. Anaesthetics i.v., thiamylal. Hypnotics barbiturate, pentobarbitone. Hypnotics barbiturate, secobarbitone. Ions, calcium.

Thiobarbiturates have been used for induction of general anaesthesia and also for brain protection in cerebral ischaemia. Although the reduction in arterial pressure after i.v. injection of thiobarbiturates may be caused mainly by suppression of sympathetic tone and cardiac contractility, barbiturates have been shown to exert direct effects on vascular smooth muscle of various origins[1–9]. Previous authors have suggested that the direct vascular effect of pentobarbitone is a result of its Ca^{2+} channel blocking action[10]. Except for our previous reports[11–13], however, there have been no investigations of the mechanism of thiobarbiturate-induced vasodilatation. In this study, we used a fluorescent indicator of cytosolic calcium concentration ([Ca^{2+}]$_i$) to determine the effect of barbiturates on [Ca^{2+}]$_i$ under basal conditions and on depolarization-induced calcium influx. We demonstrated different effects of oxybarbiturates and thiobarbiturates on [Ca^{2+}]$_i$ and calcium-contraction coupling in vascular smooth muscle.

Materials and methods

The study was approved by the Kyoto University Animal Use Committee. We studied 20 male Wistar rats (250–350 g) anaesthetized with pentobarbitone 50 mg kg^{-1} i.p. and killed by exsanguination from the common carotid arteries. The descending part of the thoracic aorta was isolated from each rat and dissected into 8–10 rings (2-mm wide). The rings were rinsed and bathed in Krebs' bicarbonate solution at 25 °C for more than 20 min until used. The rings were then bathed in Krebs' bicarbonate solution containing fluo 3-AM 10 µmol litre^{-1} [14] and 0.02% vol/vol Cremophor EL for 0.5–1 h at 25 °C. Cremophor EL is a non-cytotoxic detergent which was added to increase the solubility of fluo 3-AM[15]. After rinsing, the endothelium was removed from the luminal surface by rubbing with cotton sticks in order to exclude the influence of endothelial [Ca^{2+}]$_i$ on fluorescence intensity. The vascular rings were then mounted under a resting tension of 1 g weight, in Krebs' bicarbonate solution, maintained at 37 °C, and aerated with a mixture of 5% carbon dioxide in oxygen. They were then contracted with phenylephrine 0.1 µmol litre^{-1} and exposed to acetylcholine 10 µmol litre^{-1} which induced less than 10% of the phenylephrine-induced precontraction in all rings used[16].

Isometric tension and fluorescence intensity were recorded continuously using an Amplifier Case 7903 force-displacement transducer (San-ei, Tokyo, Japan) and a CAF-110 fluorometer (Japan Spectroscopic, Tokyo, Japan)[17]. The arterial rings were illuminated with a 75-W xenon lamp at an excitation wavelength of 490 nm, and the emitted fluorescence at 540 nm was considered to be an indicator of

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$[Ca^{2+}]_i$[14]. In our preliminary study, thiopentone 300 μmol litre^{-1} decreased the transmittance of light at wavelengths of 340 nm and 380 nm to 91.8% and 94.0%, respectively, and thiamylal to 86.5% and 96.3%. However, transmittance of 490 nm light was not significantly altered by the barbiturates tested (up to 1 mmol litre^{-1}).

In the relaxation study, vascular rings were precontracted with KCl 30 mmol litre^{-1}. When the tension and fluorescence intensity had stabilized after KCl exposure, the rings were exposed to cumulative concentrations of thiopentone or pentobarbitone (30–300 μmol litre^{-1}). The time-control was run in an identical manner but without exposure to barbiturates. The stabilized tension and fluorescence intensity after exposure to each barbiturate concentration were expressed as percentages, taking the levels before exposure to KCl as 0% and those after exposure and just before the start of barbiturate exposure as 100%.

In the contraction study, all rings were first exposed to KCl 30 mmol litre^{-1} for 5 min and then washed out. The change induced by this first exposure to KCl was taken as 100%, and the changes in tension and fluorescence intensity in the following study were expressed as values relative to this. The rings were then exposed to one of the barbiturates for 10 min or, after 5 min of pretreatment with a barbiturate, exposed to KCl 30 mmol litre^{-1} again for another 5 min. The barbiturates used were thiopentone, thiamylal, pentobarbitone and secobarbitone (30–300 μmol litre^{-1}). After washout, the rings were exposed to KCl 30 mmol litre^{-1} as a post-barbiturate control. The time-control was run in an identical manner but without barbiturates.

Krebs' bicarbonate solution contained (mmol litre^{-1}): NaCl 127.5, $NaHCO_3$ 15.5, glucose 10.0, KCl 4.6, KH_2PO_4 1.2, $MgSO_4$ 1.2 and $CaCl_2$ 2.5. Drugs used were fluo 3-AM (Dojindo Laboratories, Kumamoto, Japan), Cremophor EL (Sigma, St Louis, MO, USA), L-phenylephrine hydrochloride (Sigma), acetylcholine (Daiichi Pharmaceutical Co., Tokyo, Japan), sodium thiopentone (Tanabe Pharmaceutical, Osaka, Japan), sodium thiamylal (Kyorin Pharmaceutical, Tokyo, Japan), sodium secobarbitone (Yoshitomi Pharmaceutical, Osaka, Japan) and sodium pentobarbitone (Nacalai Tesque, Kyoto, Japan). Data in the relaxation study were analysed by Student's *t* test for unpaired data. All other data were analysed using analysis of variance and Scheffe's test. Differences were considered significant at $P<0.05$.

In the relaxation study, vascular rings were exposed to KCl 30 mmol litre^{-1} twice, and cumulative concentrations of thiopentone or pentobarbitone. The order of the experiments for the two barbiturates was randomized. In the contraction study, after the first exposure to KCl and washout, the rings were exposed to one of the barbiturates for 10 min, or exposed to KCl again for another 5 min after 5 min of pretreatment with a barbiturate. The time-controls were run in an identical manner, but without barbiturates.

Results

KCl-precontracted aortic rings were relaxed by thiopentone and pentobarbitone 100–300 μmol litre^{-1} in a concentration-dependent manner ($P<0.05$–0.01) (figs 1, 2). $[Ca^{2+}]_i$, as measured by fluorescence intensity, was decreased by pentobarbitone 300 μmol litre^{-1} ($P<0.05$), but not by thiopentone (figs 1, 2). Mean thiopentone- and pentobarbitone 300 μmol litre^{-1}-induced reductions in tension were 59.4 (SD 2.8) % and 40.7 (4.4) %, respectively, and pentobarbitone 300 μmol litre^{-1}-induced reduction in $[Ca^{2+}]_i$ was −31.2 (17.0) % (n=4, each).

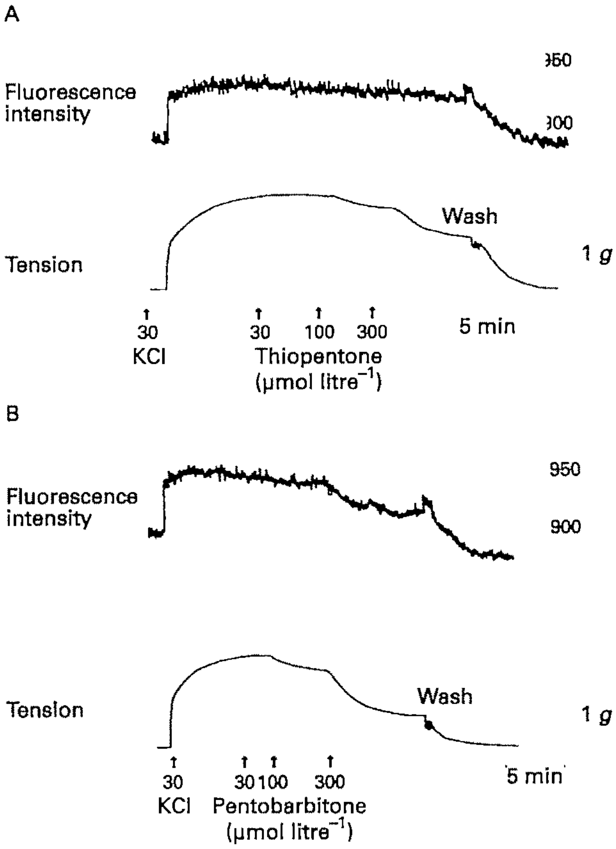


Figure 1 Representative recordings of fluorescence intensity (as an indicator of $[Ca^{2+}]_i$) and tension in rat aortic rings, which had been precontracted with KCl 30 mmol litre^{-1} and then exposed to thiopentone (A) or pentobarbitone (B) in cumulative concentrations (30–300 μmol litre^{-1}).

The tension and fluorescence intensity of aortic rings under basal conditions were increased by 10 min exposure to thiopentone and thiamylal 100–300 μmol litre^{-1} (figs 3, 4), but not to pentobarbitone or secobarbitone (up to 300 μmol litre^{-1}). The increase in tension and fluorescience intensity induced by thiopentone 300 μmol litre^{-1} was 25.1 (3.2) % and 55.0 (6.0) % of KCl 30 mmol litre^{-1}-induced changes, respectively, and those for thiamylal 300 μmol litre^{-1} were 29.1 (8.9) % and 48.5 (5.5) %, respectively.

Although the addition of KCl 30 mmol litre^{-1} to barbiturate-treated rings increased their tension and fluorescence intensity, the total increase in tension induced by KCl and barbiturates was less than in the barbiturate-untreated controls ($P<0.05$–0.01) (fig. 4). The changes in tension in the presence of thiopentone, thiamylal, pentobarbitone and secobarbitone 300 μmol litre^{-1} were 64.8 (2.5) % (n=6), 70.8 (4.2) % (n=6), 57.5 (2.2) % (n=9) and 36.6 (3.4) % (n=6), respectively.

KCl-induced increase in fluorescence intensity was decreased by pentobarbitone and secobarbitone 300 μmol litre^{-1} to 77.9 (5.2) % (n=9) and 67.3 (8.7) % (n=6), respectively ($P<0.05$). In contrast, the total

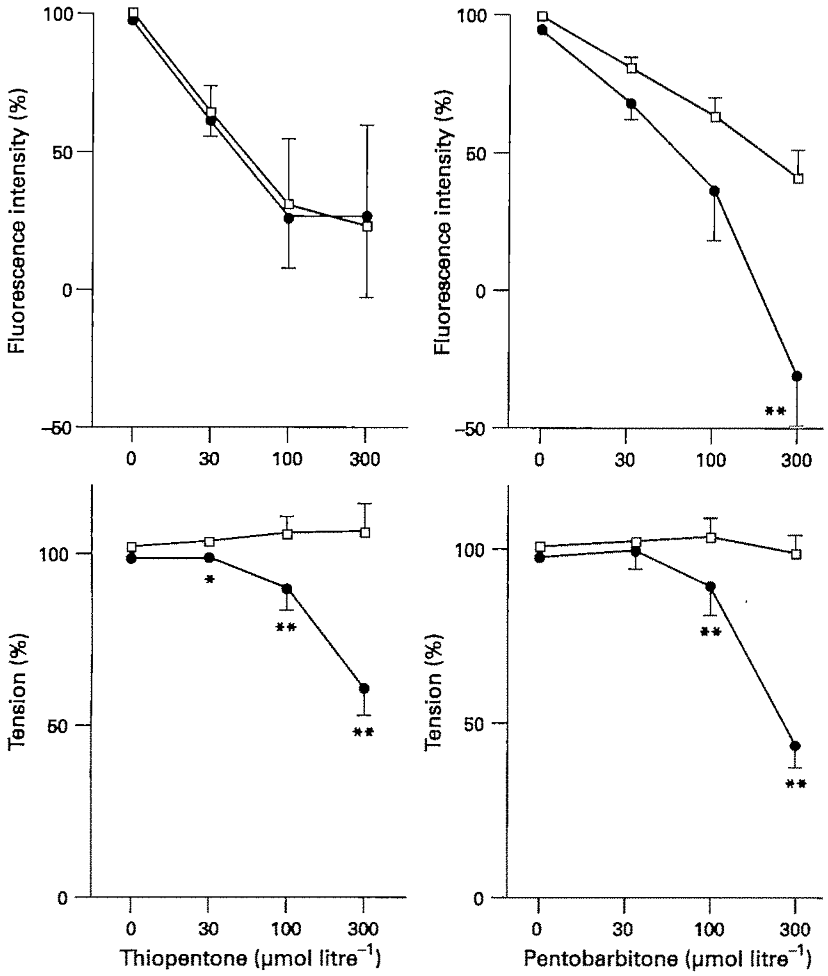


Figure 2 Changes in fluorescence intensity and tension of aortic rings precontracted with KCl 30 mmol litre^{-1}. □=Without barbiturates; ●=exposed to thiopentone or pentobarbitone at cumulative concentrations (30–300 µmol litre^{-1}). Levels before exposure to KCl 30 mmol litre^{-1} were taken as 0% and those just before exposure to barbiturates as 100%. n=4, each. *P<0.05, **P<0.01 compared with untreated control.

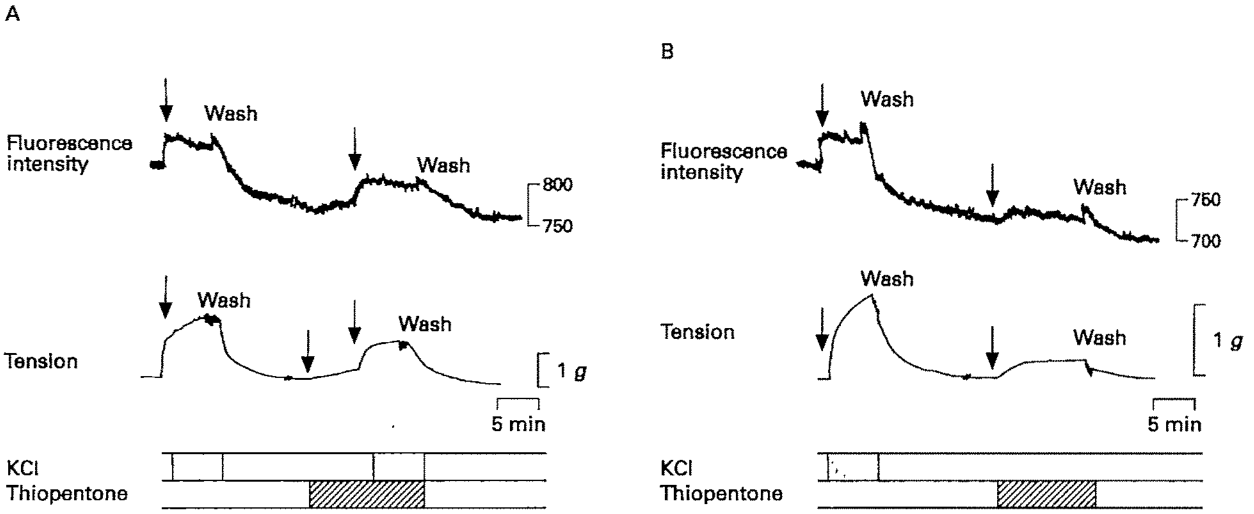


Figure 3 Representative recordings of fluorescence intensity and tension of aortic rings exposed twice to KCl 30 mmol litre^{-1} in the absence (first exposure) and presence of thiopentone 100 µmol litre^{-1} (second exposure) (A). Recordings of rings exposed to thiopentone but not to KCl are also shown (B).

increase in fluorescence intensity in rings treated with up to 300 µmol litre^{-1} of thiopentone or thiamylal was not significantly different from controls. Changes in tension and fluorescence intensity induced by the post-barbiturate and KCl-exposure were not significantly different from the pre-barbiturate control values (data not shown), indicating that the effects of the barbiturates were reversible.

Discussion

One might criticize the fact that we used pentobarbitone anaesthesia before exsanguination of rats, arguing that pentobarbitone injected i.p. would have affected the result. However, our *in vitro* results suggested that this was unlikely, because the vascular effects of barbiturates at up to 300 µmol litre^{-1} added to the bathing solution were abolished completely

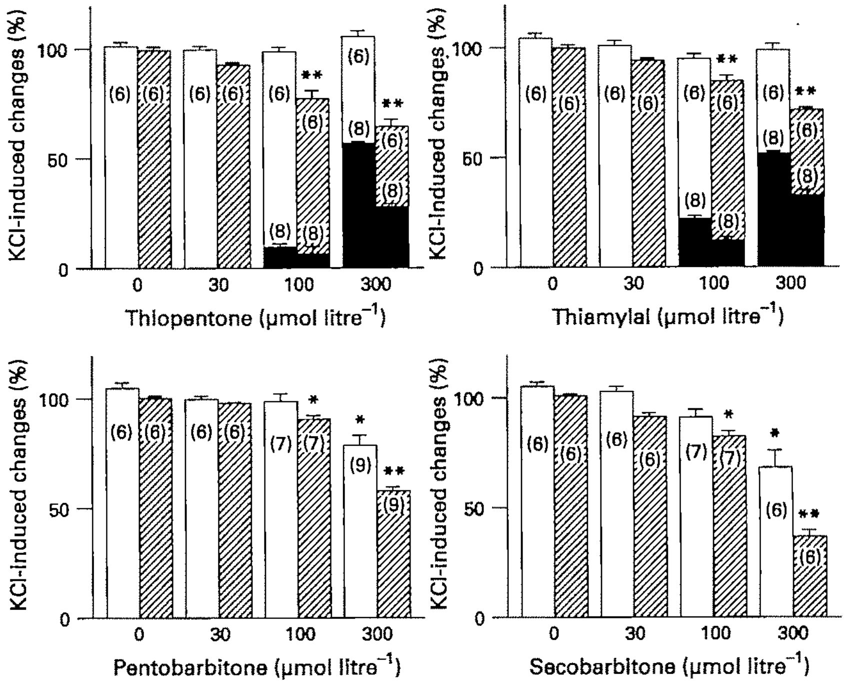


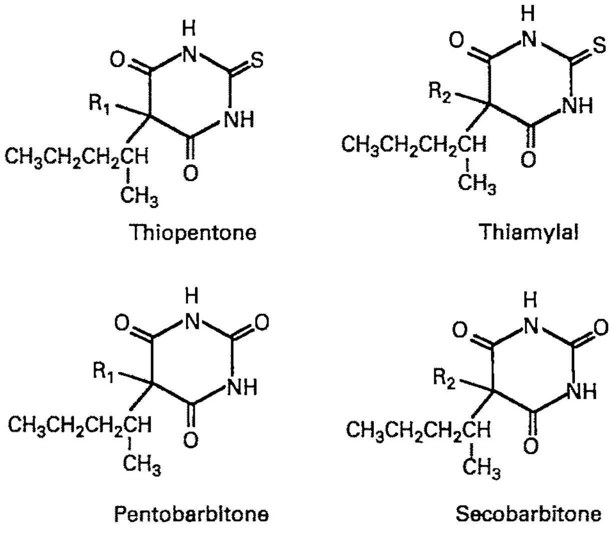
Figure 4 Changes in fluorescence intensity (open bars) and tension (hatched bars) induced by KCl 30 mmol litre^{-1} and barbiturates 30–300 μmol litre^{-1}. Solid bars=changes induced by barbiturates alone. Changes induced by the first KCl-exposure in the absence of barbiturates (pre-barbiturate controls) were taken as 100%. Values in parentheses indicate the number of rings studied. *$P<0.05$, **$P<0.01$ compared with values without barbiturates (time-controls).

after washout and the anaesthetic concentration of pentobarbitone was less than 300 μmol litre^{-1}. Also, in preliminary studies we used rats anaesthetized with both ketamine and pentobarbitone and the results obtained were similar.

Our previous studies demonstrated that thiobarbiturates, but not oxybarbiturates, exerted vasoconstrictive effects on rat aortae and canine peripheral arteries under basal conditions[7–9]. This study confirmed these findings and further demonstrated that the thiobarbiturate-induced contractions in aortic rings under basal conditions were associated with increased $[Ca^{2+}]_i$.

In contrast, in KCl-precontracted aortic rings, the thiopentone-induced decrease in tension was not associated with a reduction in $[Ca^{2+}]_i$. Moreover, although the KCl-induced contraction was smaller in thiobarbiturate-treated than in untreated rings, the KCl-induced increase in $[Ca^{2+}]_i$ did not differ between the two treatments.

Previous studies by Sanchez-Ferrer and colleagues[6] and ourselves[11–13] have shown that thiobarbiturates suppressed contractions induced by an influx of extracellular Ca^{2+} and also those caused by the release of Ca^{2+} from intracellular stores in vascular smooth muscle, including those mediated by inositol triphosphate (IP3) and calcium-induced calcium release (CICR). These results suggest two possibilities; either thiobarbiturates suppress Ca^{2+} mobilization by non-specific means or they affect some site distal to the regulation of $[Ca^{2+}]_i$. The former possibility was clearly not supported by the present finding that thiobarbiturates, at concentrations of up to 300 μmol litre^{-1}, did not decrease $[Ca^{2+}]_i$ in the presence of high K. Furthermore, the latter possibility was supported by previous reports showing that thiobarbiturates suppressed Ca^{2+}-induced contractions of chemically skinned muscle fibres from canine mesenteric artery[11 12].



Thiopentone

Thiamylal

Pentobarbitone

Secobarbitone

Figure 5 Chemical structures of thiopentone, thiamylal, pentobarbitone and secobarbitone. R1= $-CH_2CH_3$; R2=- $CH_2CH{=}CH_2$.

In contrast with the thiobarbiturates, relaxation induced by pentobarbitone was accompanied by a decrease in $[Ca^{2+}]_i$. In oxybarbiturate-pretreated rings, KCl-induced changes in $[Ca^{2+}]_i$ were smaller than in control rings. These findings concur with those of previous authors[10] and ourselves using these compounds[12 13]. Therefore we speculate that oxybarbiturates suppress depolarization-induced calcium influx, although the possibility that they also affect some site distal to calcium mobilization cannot be excluded.

Except for substitution of an oxygen atom for sulphur on the second carbon atom, thiopentone has the same chemical structure as pentobarbitone, and thiamylal the same as secobarbitone (fig. 5). Thus we postulate that thiobarbiturates and oxybarbiturates, at concentrations of up to 300 μmol litre^{-1}, have different effects on smooth muscle from rat aorta; only thiobarbiturates increased $[\mathrm{Ca}^{2+}]_i$ to constrict rat aorta under basal conditions, whereas only oxybarbiturates decreased $[\mathrm{Ca}^{2+}]_i$ in KCl-contracted rat aorta. In addition to their effects on $[\mathrm{Ca}^{2+}]_i$, thiobarbiturates seemed to affect some site distal to the regulation of $[\mathrm{Ca}^{2+}]_i$, such as calmodulin, the phosphorylation or dephosphorylation process of myosin light chain (MLC), or the contractile machinery itself.

The peak plasma concentration of thiobarbiturates after induction of anaesthesia is 100–300 μmol litre^{-1}, and as more than 85% is bound to plasma proteins, the concentration of the unbound form is less than 50 μmol litre^{-1} [18,19]. Therefore, the effective concentrations of thiobarbiturates in this study were not much higher than those that are found clinically.

In summary, we found that thiobarbiturates relaxed vascular smooth muscle isolated from rat aorta independently of $[\mathrm{Ca}^{2+}]_i$, while oxybarbiturates reduced both tension and $[\mathrm{Ca}^{2+}]_i$. In regulating vascular smooth muscle tone, thiobarbiturates seemed to affect sites distal to the regulation of $[\mathrm{Ca}^{2+}]_i$.

References

1. Price ML, Price HL. Effects of general anesthetics on contractile responses of rabbit aortic strips. *Anesthesiology* 1962; **23**: 16–20.
2. Altura BT, Altura BM. Barbiturates and aortic and venous smooth-muscle function. *Anesthesiology* 1975; **43**: 432–444.
3. Clark SC, MacCannell KL. Vascular responses to anaesthetic agents. *Canadian Anaesthetists Society Journal* 1975; **22**: 20–33.
4. Edney SM, Downes H. Contractor effect of barbiturates on smooth muscle. *Archives Internationales de Pharmacodynamie et de Therapie* 1975; **217**: 180–196.
5. Fukuda S, Inomata I, Tsuji T, Takeshita H. Thiopental potentiation of isolated rabbit pulmonary artery contractions with alpha receptor agonists. *Anesthesiology* 1984; **60**: 187–192.
6. Sanchez-Ferrer CF, Martin J, Salaices M, Rico ML, Munoz-Blanco JL. Interference of pentobarbital and thiopental with the vascular contraction and noradrenaline release in human cerebral arteries. *General Pharmacology* 1985; **16**: 469–473.
7. Hatano Y, Nakamura K, Moriyama S, Mori K, Toda N. The contractile responses of isolated dog cerebral and extracerebral arteries to oxybarbiturates and thiobarbiturates. *Anesthesiology* 1989; **71**: 80–86.
8. Moriyama S, Nakamura K, Hatano Y, Harioka T, Mori K. Responses to barbiturates of isolated dog cerebral and mesenteric arteries contracted with KCl and prostaglandin $F_{2\alpha}$. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 523–529.
9. Nakamura K, Hatano Y, Nishiwada M, Yakushiji T, Park JW, Mori K. Effects of thiobarbiturates on smooth muscle reactivity in isolated aortas from spontaneously hypertensive rats. *Anesthesia and Analgesia* 1990; **70**: 267–274.
10. Altura BA, Turlapaty PDMV, Altura BM. Pentobarbital sodium inhibits calcium uptake in vascular smooth muscle. *Biochimica et Biophysica Acta* 1980; **595**: 309–312.
11. Nakamura K, Hatano Y, Nishiwada M, Mori K. The vasodilator effect of thiamylal in dog mesenteric artery: contribution of intracellular action. *Canadian Journal of Physiology and Pharmacology* 1991; **69**: 1163–1167.
12. Yakushiji T, Nakamura K, Hatano Y, Mori K. Comparison of the vasodilator effects of thiopentone and pentobarbitone. *Canadian Journal of Anaesthesia* 1992; **39**: 604–609.
13. Nishiwada M, Nakamura K, Hatano Y, Mori K. The relaxing effects of barbiturates in vascular smooth muscle of rat aorta. *Journal of Anesthesia* 1991; **5**: 380–387.
14. Kao JPY, Harootunian AT, Tsien RY. Photochemically generated cytosolic pulses and their detection by fluo-3. *Journal of Biological Chemistry* 1989; **264**: 8179–8184.
15. Sato K, Ozaki H, Karaki H. Changes in cytosolic calcium level in vascular smooth muscle strip measured simultaneously with contraction using fluorescent calcium indicator Fura 2. *Journal of Pharmacology and Experimental Therapeutics* 1988; **246**: 294–300.
16. Furchgott RF. Role of endothelium in responses of vascular smooth muscle. *Circulation Research* 1983; **53**: 557–573.
17. Kakuyama M, Hatano Y, Nakamura K, Toda H, Terasako K, Nishiwada M, Mori K. Halothane and enflurane constrict canine mesenteric arteries by releasing Ca^{2+} from intracellular Ca^{2+} stores. *Anesthesiology* 1994; **80**: 1120–1127.
18. Becker KE. Plasma levels of thiopental necessary for anesthesia. *Anesthesiology* 1978; **49**: 192–196.
19. Burch PG, Stanski DR. The role of metabolism and protein binding in thiopental anesthesia. *Anesthesiology* 1983; **58**: 146–152.

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Comparative actions of propofol and thiopentone on cell membranes of isolated guineapig ventricular myocytes

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Summary

We have examined the effects of propofol and thiopentone on membrane potentials and currents of isolated guineapig ventricular myocytes using the whole-cell patch-clamp technique. After current clamping, propofol at concentrations greater than 0.5 μmol litre^{-1} shortened the plateau and action potential duration (APD) ($P<0.05$). Thiopentone 10 μmol litre^{-1} prolonged APD ($P<0.05$), whereas concentrations of 50 μmol litre^{-1} or higher decreased plateau height ($P<0.05$) and resting membrane potential (RMP) ($P<0.05$) with abbreviation of the prolonged APD. With voltage clamping, propofol 1 μmol litre^{-1} decreased the L-type Ca^{2+} current ($I_{Ca.L}$) to 88.4% of control ($P<0.01$) without affecting the delayed rectifier K$^+$ current (I_K) and propofol 10 μmol litre^{-1} decreased $I_{Ca.L}$ and I_K to 75.0% ($P<0.01$) and 78.4% ($P<0.01$), respectively, with no effect on the inward rectifier K$^+$ current (I_{K1}). Thiopentone 10 μmol litre^{-1} decreased $I_{Ca.L}$ to 88.5% ($P<0.01$) and I_K to 78.3% ($P<0.05$), while thiopentone 100 μmol litre^{-1} depressed $I_{Ca.L}$ to 82.8% ($P<0.01$), I_K to 27.0% ($P<0.01$) and I_{K1} to 67.3% ($P<0.05$). These results indicated that propofol, at concentrations greater than those that are clinically relevant, shortened APD mainly by suppression of $I_{Ca.L}$, and the biphasic effects on APD by thiopentone were caused by depression of I_K, and concomitant suppression of $I_{Ca.L}$ and I_{K1} at higher concentrations. The distinct cardiodepressant effects of propofol and thiopentone may be, at least in part, attributed to different actions on membrane Ca^{2+} and K$^+$ currents. (*Br. J. Anaesth.* 1996;**77**:508–516)

Key words

Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Heart, myocytes. Ions, calcium. Ions, potassium. Ions, ion channels. Heart, isolated preparation. Guineapig.

Propofol is a useful anaesthetic as an induction and maintenance hypnotic agent because of its rapid onset, short duration of action and rapid elimination[1]; its disadvantages include depression of systemic arterial pressure or heart rate, or both[2]. Several studies have demonstrated that propofol directly suppresses myocardial contractility evaluated by tension development in multicellular preparations[3-6]. Thiopentone also has been known to depress cardiac contractility[4,6-9] and to have both arrhythmogenic and antiarrhythmic actions[10].

It remains controversial as to which is the more potent negative inotropic and pro- or antiarrhythmic drug, because previous studies *in vitro* have focused mainly on trans-sarcolemmal Ca^{2+} influx and sarcoplasmic reticulum function[3,5,9,11]. In single ventricular myocytes, propofol at relatively high concentrations has been shown to shorten action potential duration (APD)[5] and suppress delayed rectifier K$^+$ currents (I_K)[12] and L-type calcium currents ($I_{Ca.L}$)[5,13] without affecting the inward rectifier K$^+$ current (I_{K1})[12]. In contrast, thiopentone has been shown to induce prolongation of APD in multicellular preparations[4,6,8,14], and to suppress $I_{Ca.L}$[15], I_K and I_{K1}[16] in single myocytes, suggesting that propofol and thiopentone have different actions on membrane currents.

Because I_{K1} and I_K together with $I_{Ca.L}$ regulate APD by determining repolarization of action potentials, modification of any one of these currents could alter contractile function and refractory period. Knowledge of the precise actions of propofol and thiopentone on repolarizing currents at therapeutic concentrations should aid understanding of their inotropic and chronotropic effects. Therefore, we assessed the comparative actions of propofol and thiopentone on membrane currents forming the repolarization phase of action potentials of isolated guineapig ventricular myocytes.

Materials and methods

The experimental procedure was approved by the Animal Care and Use Committee of Tokyo Medical and Dental University. Single ventricular myocytes were isolated from guineapig hearts by enzymatic dissociation, as described previously[17]. Briefly, animals weighing 300–400 g were anaesthetized with sodium pentobarbitone 40–50 mg kg^{-1} i.p. after heparinization (300 u. kg^{-1} i.v.). The chest was opened during artificial ventilation and the aorta was cannulated *in situ* and then perfused with Tyrode's solution before the heart was dissected out. Using a Langendorff apparatus, the heart was perfused retrogradely at 37 °C with low-Ca^{2+} (30 μmol litre^{-1}) Tyrode's solution, followed by perfusion with 0.04% collagenase (type 1, Sigma Chemical Co., St Louis, MO, USA) dissolved in low-Ca^{2+} Tyrode's solution

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for about 20 min. Single cells were obtained by gentle agitation of small pieces of ventricular tissue in a beaker containing the high-K^+, low-Cl solution (KB medium[16]) and stored at 4 °C. The preparations were transferred to a recording chamber filled with bath solution (normal Tyrode), which was placed on the stage of an inverted phasecontrast microscope (Diaphot TMD, Nikon, Tokyo, Japan). A single isolated cell with a smooth surface and clear striations was selected for electrical measurements. Electrophysiological experiments were performed within 12 h of cell isolation.

Test solutions of propofol (2,6-diisopropylphenol; Zeneca, Macclesfield, UK) were obtained by adding appropriate amounts of an aqueous emulsion (1% (w/v) propofol in 10% (w/v) soya bean oil, 1.2% (w/v) egg phosphatide and 2.25% (w/v) glycerol) to normal Tyrode's solution. Thiopentone (5-ethyl-5(1-methyl butyl)2-thiobarbiturate; Tanabe Pharmaceut Co., Osaka, Japan) was prepared freshly before every experiment. This agent was also diluted in normal Tyrode's solution to obtain the final concentrations indicated in the text. All anaesthetic concentrations in this study, therefore, are expressed as free concentrations in aqueous solution.

The composition of normal Tyrode's solution used in cell dissociation and the bath solution was (mmol litre^{-1}): NaCl 144, NaH_2PO_4 0.33, KCl 4.0, $CaCl_2$ 1.8, $MgCl_2$ 0.53, glucose 5.5 and HEPES 5.0, and the pH was adjusted to 7.3–7.4 by adding NaOH. The high-K^+, low-Cl solution had the following composition (mmol litre^{-1}): K-glutamate 70, taurine 15, KCl 30, KH_2PO_4 10, $MgCl_2$ 0.5, glucose 11, EGTA 0.5 and HEPES 10, and the pH was adjusted to 7.4 by adding KOH. The composition of the pipette solution used in recording action potentials and membrane currents was (mmol litre^{-1}): KCl 130, K_2ATP 5.0, creatine phosphate 5.0, EGTA 0.2 and HEPES 5.0, and the pH was adjusted to 7.2 with KOH. For isolation of $I_{Ca.L}$, the pipette solution replacing internal K^+ with Cs^+ and a TEA-rich external solution for Na^+ were used. The TEA-rich solution contained (mmol litre^{-1}): TEA-Cl 154.0, $CaCl_2$ 2.0, $MgCl_2$ 2.0, glucose 10.0 and HEPES 10.0, and the pH was adjusted to 7.4 with TEA-OH. The pipette solution contained (mmol litre^{-1}): CsCl 110.0, TEA-Cl 20.0, $CaCl_2$ 0.068, $MgCl_2$ 4.0, BAPTA 5.0, HEPES 10.0, K_2ATP 5.0 and cAMP 3.0, and the pH was adjusted to 7.2 with CsOH.

The whole-cell variation of the patch-clamp technique was used to record action potentials and membrane currents using an amplifier (Axopatch 1C, Axon Instruments, Foster City, CA, USA) and low-pass filtered at 10 kHz. Action potentials and membrane currents were recorded under whole-cell current-clamp and voltage-clamp modes, respectively. Acquisition and analysis of the data, and generation of the stimulus procedure, were performed with the pCLAMP software package (version 5.5.1; Axon Instruments). The temperature of the perfusion chamber was maintained at 35–36 °C. At the beginning and end of each experiment, the junction potentials between the pipette and bath solutions were checked and if differences in the two values were more than 2 mV, membrane potential was corrected accordingly. The resistance of the pipette filled with standard pipette solution was 2–4 MΩ. Test solution was applied to the bath solution at concentrations indicated in the text for 5–10 min of the observation. The washout data were observed 15 min after removal of the drug from the bath solution. Some depression of membrane currents after administration of drug may result from "rundown", and therefore data were excluded if washing with control solution did not yield recovery to at least 80% of control.

To examine the kinetics of $I_{Ca.L}$ produced by the drug, the time course of development was assessed by a curve-fitting procedure using a simple non-linear least-squares algorithm on a personal computer (IBM-AT). The formula for the curve fitting used in this study is:

$I_{Ca.L}=A_1\exp(-bC_1)+A_2\exp(-bC_2)+A_3\exp(-bC_3)+A$

where b=pulse number or time, and C_1, C_2 and C_3=onset rates. Applicability of either one, two or three exponential functions was always examined using the F test.

All values are expressed as mean (SEM). Statistical significance of a drug treatment was determined by paired or unpaired Student's t test; $P<0.05$ was considered significant, except in the F test where $P<0.01$ was significant.

Results

EFFECTS OF PROPOFOL AND THIOPENTONE ON ACTION POTENTIALS

Propofol 0.1 μmol litre^{-1} had no effect on action potential variables (n=4, fig. 1A). Propofol shortened APD at 90% repolarization (APD_{90}) at concentrations of 0.5 μmol litre^{-1} or greater ($P<0.05$). At concentrations of 1 μmol litre^{-1} or higher, propofol shortened APD at 20% repolarization (APD_{20}) ($P<0.05$). Propofol changed neither action potential amplitude (APA) nor resting membrane potential (RMP) (fig. 1A, table 1). Administration of the vehicle alone (0.002% Intralipid; Otsuka Pharmaceutical Co., Tokyo, Japan), in an amount equal to that contained in propofol 10 μmol litre^{-1}, did not significantly affect action potential variables (n=5, data not shown).

Administration of thiopentone 1 μmol litre^{-1} had little effect on APD_{20} or APD_{90}. Thiopentone 10 μmol litre^{-1} induced prolongation of APD_{90} (n=5, $P<0.05$) without change in APD_{20} (table 1). At 50 and 100 μmol litre^{-1}, thiopentone caused a decrease in RMP ($P<0.05$) and shortened APD_{20} ($P<0.05$). The prolonged APD_{90} was abbreviated by thiopentone 50 and 100 μmol litre^{-1}; values were almost the same as those of the control (fig. 1B, table 1).

EFFECTS OF PROPOFOL AND THIOPENTONE ON MEMBRANE CURRENTS

Figure 2 shows the changes in current–voltage relationships (A) and current traces (B) induced by the two agents. At concentrations of 1 μmol litre^{-1} or higher, propofol had almost no observable effects on the late current at potentials negative to −30 mV, which reversed its polarity at about −90 mV. Propofol decreased the late current at voltages positive to −30 mV. These results suggest that propofol reduced I_K but had no detectable effect on I_{K1}. In addition, propofol depressed the initial peak inward current on depolarization from −30 mV without change in its reversal potential.

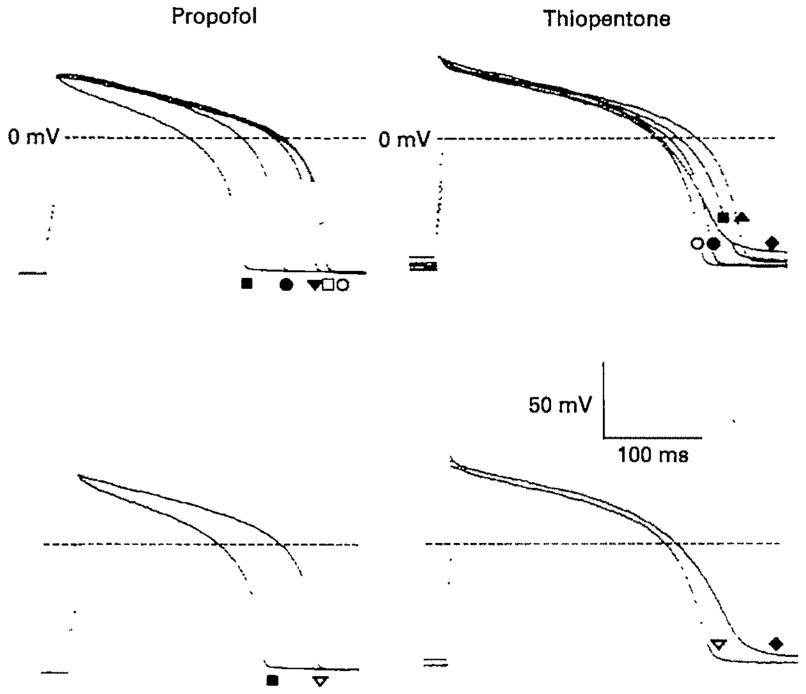

Figure 1 Effects of propofol and thiopentone on action potentials. Action potentials were elicited by applying rectangular pulses with a 5-ms duration at a frequency of 0.2 Hz to ventricular myocytes, 5–6 min after achieving the whole-cell current-clamp and their configurations became stable. Propofol and thiopentone were then applied to the bath solution at concentrations of 0.1 (□), 0.5 (▼), 1 (●), 10 (▲) and 50 (■) μmol litre^{-1} and 1 (●), 10 (▲), 50 (■) and 100 (◆) μmol litre^{-1} in a successive manner, respectively. O= Control. ▽= Washout of drug. Action potentials were recorded from a single preparation.

Table 1 Effects of propofol and thiopentone on variables of the action potential in guineapig ventricular myocytes (mean (SEM)). C = control, P = propofol, T = thiopentone, W = washout, RMP = resting membrane potential, APA = action potential amplitude. *$P < 0.05$, ** $P < 0.01$ *vs* control; † $P < 0.05$, †† $P < 0.01$ *vs* drug

	n		RMP (mV)	APA (mV)	APD$_{20}$ (ms)	APD$_{90}$ (ms)
Propofol (μmol litre^{-1})						
		C	−84.8 (1.2)	135.8 (2.6)	157.8 (7.3)	253.9 (11.2)
0.5	5	P	−85.4 (3.2)	133.0 (3.3)	147.8 (10.8)	235.0 (10.5)*
		W	−85.8 (2.3)	132.4 (4.0)	153.8 (7.7)	243.8 (10.2)
		C	−84.4 (0.9)	137.5 (0.9)	150.2 (9.9)	248.1 (12.2)
1	11	P	−81.5 (1.0)	136.3 (1.1)	124.8 (15.0)*	211.7 (16.1)**
		W	−82.9 (1.0)	137.1 (1.2)	141.7 (10.0)	235.2 (14.0)††
		C	−84.2 (0.9)	132.0 (2.2)	156.4 (10.4)	245.3 (14.6)
10	7	P	−83.2 (1.1)	130.9 (2.2)	124.0 (16.1)*	206.1 (17.8)**
		W	−83.2 (1.1)	131.6 (2.0)	150.2 (7.4)†	237.7 (8.1)††
		C	−84.2 (2.0)	134.8 (2.1)	151.4 (16.2)	246.4 (23.7)
50	8	P	−82.0 (2.5)	133.9 (2.2)	109.4 (25.7)**	196.7 (34.6)**
		W	−83.0 (2.4)	135.0 (2.1)	143.5 (18.8)††	237.4 (25.8)††
Thiopentone (μmol litre^{-1})						
		C	−84.5 (2.0)	136.4 (1.3)	171.2 (24.1)	277.5 (28.2)
1	4	P	−84.8 (2.4)	136.8 (1.3)	188.6 (19.5)	295.7 (23.6)
		W	−85.1 (2.1)	135.5 (1.2)	170.4 (21.8)	276.5 (25.3)
		C	−84.2 (2.0)	135.6 (1.4)	161.7 (21.0)	263.2 (22.0)
10	5	P	−82.6 (2.3)	136.1 (1.6)	187.5 (17.7)	297.2 (23.6)*
		W	−83.2 (2.2)	134.9 (1.3)	163.4 (20.0)	263.4 (19.5)†
		C	−83.8 (2.1)	136.9 (1.1)	183.6 (37.4)	254.2 (26.6)
50	4	P	−77.4 (3.7)*	134.5 (2.2)	156.4 (41.0)*	271.8 (33.5)
		W	−77.7 (3.9)	135.0 (0.8)	170.0 (36.8)†	238.2 (25.8)
		C	−83.7 (1.6)	134.9 (1.1)	172.5 (37.7)	270.8 (42.2)
100	4	P	−73.8 (2.3)**	129.4 (3.6)	136.3 (30.1)*	269.7 (36.1)
		W	−76.9 (1.9)	134.4 (1.4)	155.9 (34.1)†	250.0 (38.4)

At concentrations of 10 μmol litre^{-1} or higher, thiopentone suppressed the late current at all voltages tested, suggesting that thiopentone depresses both I_{K1} and I_K. Thiopentone decreased the late current at test pulses to −110 mV to 89.2 (1.9) % (10 μmol litre^{-1}; ns *vs* control as 100%), 82.7 (5.5) % (50 μmol

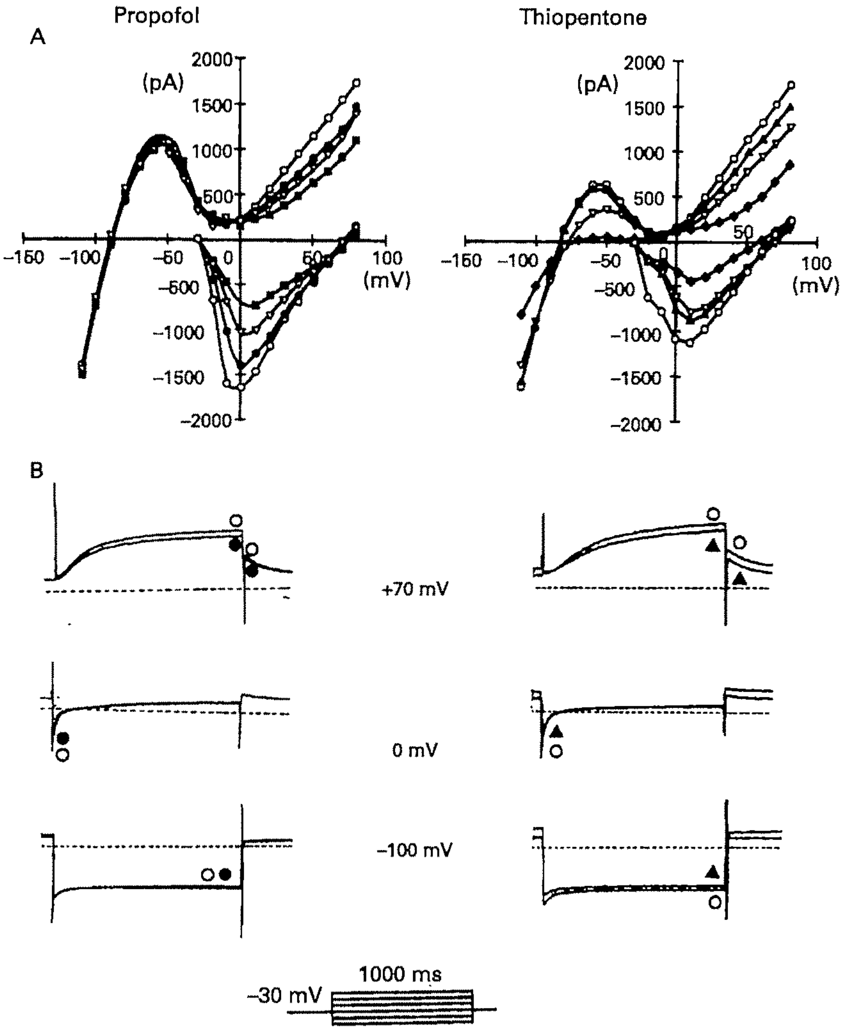

Figure 2 Effects of propofol and thiopentone on membrane currents. (A) Current–voltage relationship. Membrane currents were elicited by depolarizing or hyperpolarizing voltage steps from the holding potential of −30 mV for 1000 ms at 0.1 Hz. The late current was measured by the current level at the end of test pulses. The peak inward current was measured as the difference between the initial peak inward current on depolarizing and the control holding current level. O=Control. ●= Drug 1 μmol litre^{-1}; ▲=drug 10 μmol litre^{-1}; ■=drug 50 μmol litre^{-1}; ◆=drug 100 μmol litre^{-1}; ∇=washout. (B) Current traces in the absence (O) and presence of propofol 1 μmol litre^{-1} (●) or thiopentone 10 μmol litre^{-1} (▲) were superimposed at each voltage step (mV).

litre^{-1}; $P<0.05$) and 67.3 (8.0) % (100 μmol litre^{-1}; $P<0.05$) ($n=5$). After washout of thiopentone 100 μmol litre^{-1}, the current recovered to 89.1 (3.1) % of control ($n=5$; $P<0.05$ *vs* 100 μmol litre^{-1}). The late current positive to −30 mV was decreased by the drug. Thiopentone also suppressed the initial peak current on depolarization from −30 mV.

EFFECTS OF PROPOFOL AND THIOPENTONE ON $I_{Ca.L}$

Propofol and thiopentone decreased the initial peak inward current on depolarization (fig. 2), suggesting suppression of $I_{Ca.L}$. Therefore, we examined the effects of these agents on isolated $I_{Ca.L}$ (fig. 3). The amplitude of $I_{Ca.L}$ was decreased to 88.4 (1.8) % by propofol 1 μmol litre^{-1} ($n=5$; $P<0.01$ *vs* control as 100%) and 75.0 (5.3) % at propofol 10 μmol litre^{-1} ($n=5$; $P<0.01$) at a frequency of 0.2 Hz. The currents recovered to 87.8 (2.8) % ($P<0.05$ *vs* 10 μmol litre^{-1}) after washout of propofol 10 μmol litre^{-1}. Administration of thiopentone 10 and 100 μmol litre^{-1} decreased $I_{Ca.L}$ to 88.5 (1.2) % ($n=5$; $P<0.01$ *vs* control as 100%) and 82.8 (1.6) % ($n=5$; $P<0.01$), respectively. After washout of thiopentone 100 μmol litre^{-1}, the current recovered to 89.7 (2.4) % of control ($P<0.01$ *vs* 100 μmol litre^{-1}) (fig.3A).

Use-dependent block of $I_{Ca.L}$ by propofol and thiopentone was examined by applying 11 depolarizing pulses at 0.2 Hz or 50 pulses at 1 Hz (fig.3B). In the absence of drug (control), the currents at the 11th (0.2 Hz) or 50th (1 Hz) pulse were decreased by 6% or less of the first pulse of $I_{Ca.L}$. Thus steady-state $I_{Ca.L}$ was 94% or the higher of the current as the first pulse. In the presence of propofol 1 μmol litre^{-1}, $I_{Ca.L}$ at the 11th pulse at 0.2 Hz was decreased to 91.8 (1.0) % of the current at the first pulse ($P<0.01$; $n=4$). The current at the 50th pulse at 1 Hz was decreased to 60.0 (4.9) % ($P<0.05$; $n=4$). In the presence of thiopentone 10 μmol litre^{-1}, $I_{Ca.L}$ at the 11th pulse at 0.2 Hz was suppressed to 90.0 (2.0) % of the first pulse ($P<0.05$; $n=4$) and the current at the 50th at 1 Hz was 68.0 (5.3) % of the first pulse ($P<0.05$; $n=4$). Therefore, both drugs produced use-dependent block of $I_{Ca.L}$.

EFFECTS OF PROPOFOL AND THIOPENTONE ON THE KINETICS OF $I_{Ca.L}$

The inactivation time course of $I_{Ca.L}$ was analysed using the current evoked by depolarization to +10 mV at 0.2 Hz with the voltage procedure similar to figure 3B. The time course of the current was well fit-

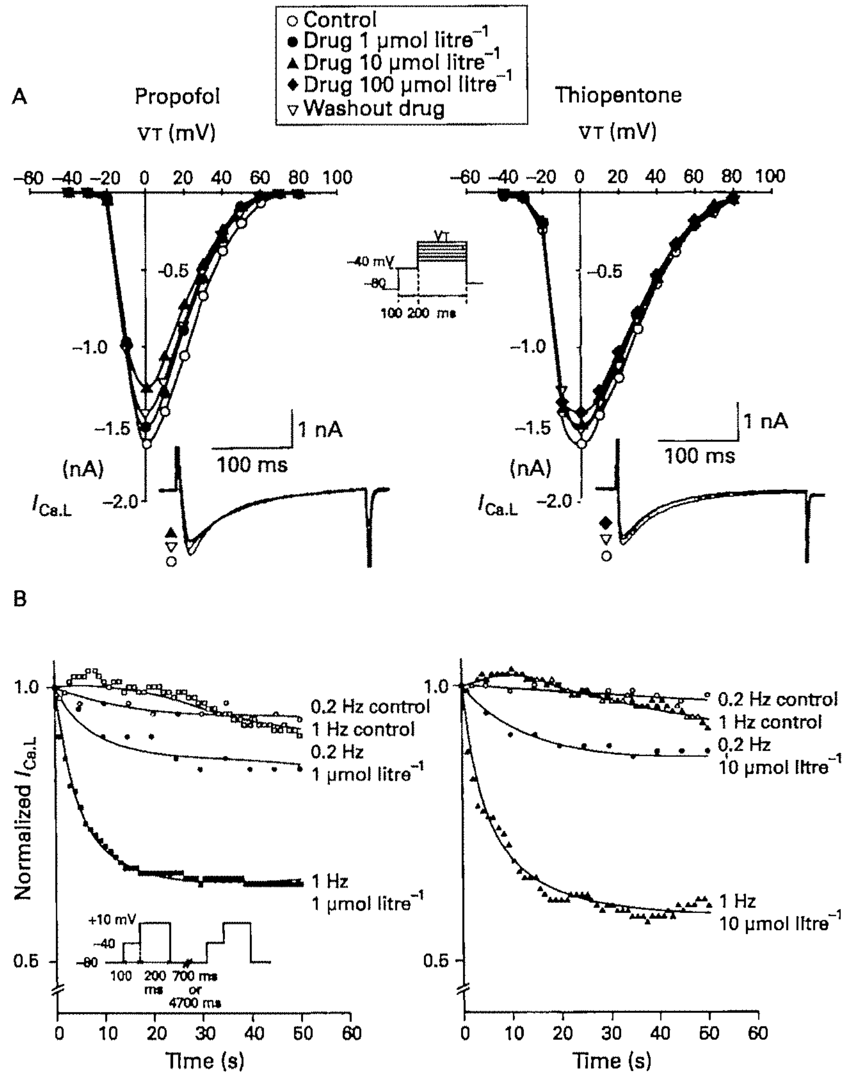

Figure 3 Effects of propofol and thiopentone on $I_{Ca.L}$. (A) Current–voltage relationship. $I_{Ca.L}$ were activated by stepping to different depolarized levels in 10-mV increments for 200 ms after the conditioning pulse to −40 mV for 100 ms from the holding potential of −80 mV to inactivate the fast Na^+ and T-type Ca^{2+} currents. The current traces of $I_{Ca.L}$ (inset) were evoked at test potential to 0 mV. (B) Use-dependent block of $I_{Ca.L}$ was examined by applying test pulses at 0.2 Hz or 1.0 Hz for periods of 50 s. $I_{Ca.L}$ evoked by the test pulse consisted of 200ms depolarizing pulses to +10 mV preceded by 100-ms depolarizations to −40 mV from a holding potential of −80 mV. The current amplitudes were normalized to the current amplitude of the first pulse.

ted to the sum of two exponentials with the fast (τ fast; 9.0 (1.8) ms) and slow (τ slow; 64.0 (4.8) ms) time constants in the control (n=7). Administration of propofol 1 and 10 µmol litre^{-1} increased τ fast to 10.1 (1.8) ms (P<0.05) and 12.6 (2.0) ms (P<0.01), respectively, with no change in τ slow. In contrast, thiopentone 10 and 100 µmol litre^{-1} decreased τ slow from 66.4 (3.6) ms in the control (n=12) to 57.1 (3.4) ms (P<0.01) and 49.0 (3.6) ms (P<0.01), respectively, without affecting τ fast. Washout of thiopentone reversed τ slow to 60.6 (5.1) ms (P<0.01 *vs* thiopentone 100 µmol litre^{-1}).

Effects of the drugs on steady-state inactivation and activation processes of $I_{Ca.L}$ were evaluated. Steady-state inactivation curves (f_∞) were drawn by least-square fitting to the empirical Boltzmann equation to the mean values from each group of data:

$$f_\infty=1/(1+\exp((Vm-Vh)/s))$$

where Vm=pre-pulse potential, Vh=membrane voltage at which $I_{Ca.L}$ is half maximal, and s=slope factor. Under control conditions, Vh and s were −19.4 (0.2) mV and 5.7 (0.2) mV, respectively (n=5). These values did not change significantly during administrations of drugs (fig. 4A).

Steady-state activation curves (d_∞) were drawn by fitting the Boltzmann equation to data points of the mean values:

$$d_\infty=1-1/(1+\exp((Vm-Vh)/s))$$

where Vm=membrane voltage, Vh=voltage, where the current amplitude is half maximal, and s=slope factor. Control values of Vh and s were -8.2 (0.4) mV and 8.9 (0.4) mV, respectively (n=5). Neither anaesthetic had any effect on these variables (fig. 4B).

We investigated the effects of propofol and thiopentone on recovery from inactivation of $I_{Ca.L}$ using a double pulse design. Under control conditions the recovery process was well fitted to a single exponential with a time constant of 84.6 (16.4) ms. In the presence of propofol 1 µmol litre^{-1}, the time constant increased to 142.4 (22.9) ms (P<0.05; n=7). Similarly, thiopentone 10 µmol litre^{-1} increased it from a control value of 77.4 (22.6) ms to 106.1 (24.3) ms (P<0.05; n=5)(fig. 4C).

EFFECTS OF PROPOFOL AND THIOPENTONE ON THE DELAYED RECTIFIER K^+ CURRENT

The drug effects on I_K were estimated by measuring

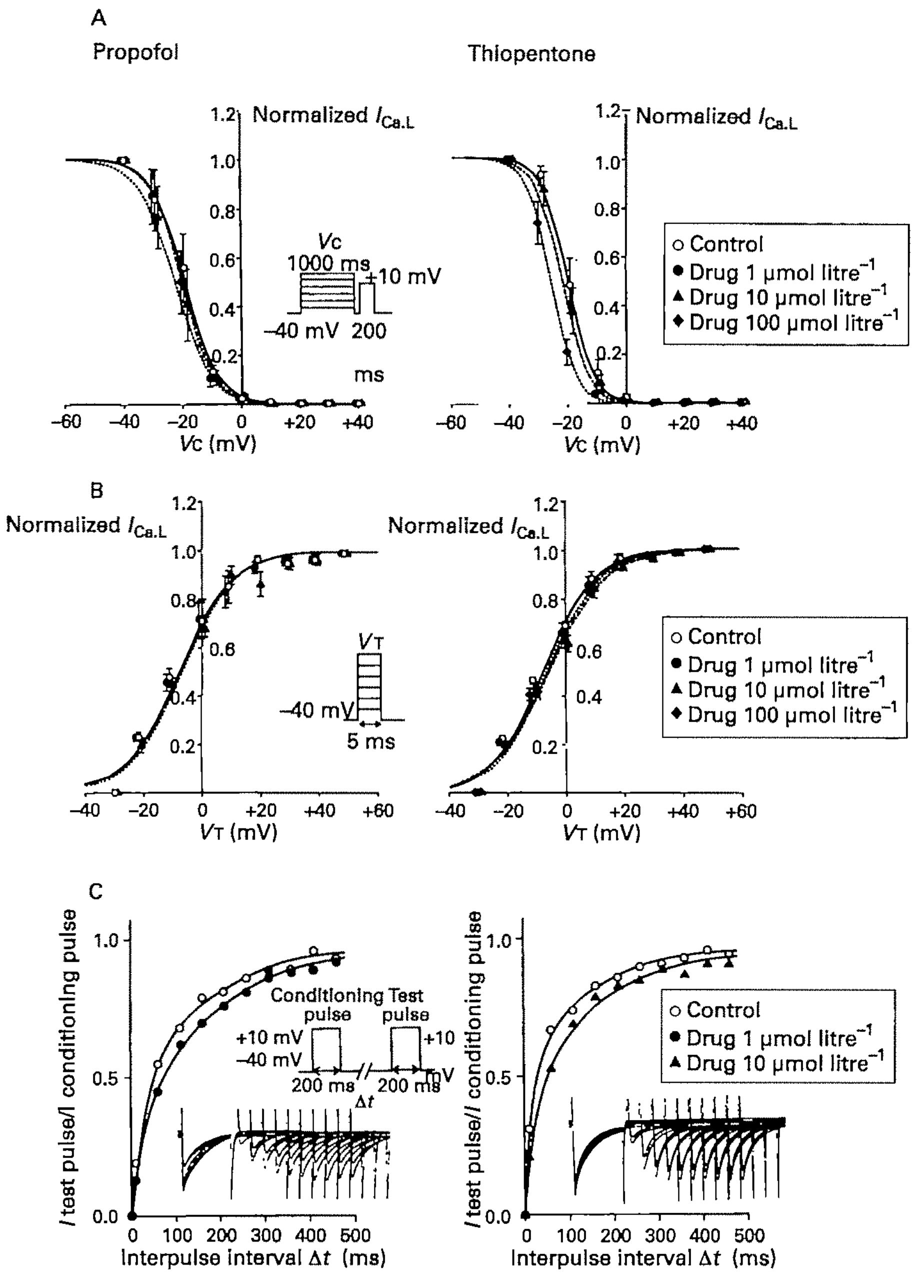

Figure 4 Effects of propofol and thiopentone on changes in the kinetics of $I_{Ca.L}$. (A) Steady-state inactivation of $I_{Ca.L}$ was assessed by applying conditioning pre-pulses for 1000 ms in 10-mV increments from −30 mV, followed by 200 ms test pulses to +10 mV preceded by a 4-ms return to the holding potential of −40 mV, and normalized $I_{Ca.L}$ was plotted as function of pre-pulse voltage. (B) Steady-state activation of $I_{Ca.L}$ was measured by the inward tail current elicited by depolarizing test pulses of 5 ms duration from a holding potential of −40 mV to +50 mV by 10-mV increment. (C) Effects of propofol and thiopentone on recovery from inactivation of $I_{Ca.L}$. The current amplitude evoked by test pulses to +10 mV for 200 ms was elicited after various diastolic intervals ranging from 10 to 1500 ms at −40 mV, following the conditioning pulse for 200 ms to +10 mV.

the tail current of I_K ($I_{K.tail}$) on repolarization to −30 mV. Steady-state activation of $I_{K.tail}$ and the drug effects are shown in figure 5 (inset). During administration of propofol 1 μmol litre^{-1}, $I_{K.tail}$ did not change from control, but propofol 10 μmol litre^{-1} significantly suppressed the current. $I_{K.tail}$ at test pulses to +80 mV was decreased to 78.4 (4.0)% of control ($P<0.01$; $n=6$) in the presence of propofol 10 μmol litre^{-1}. Administration of thiopentone 10 and 100 μmol litre^{-1} significantly decreased $I_{K.tail}$ at test pulses to +80 mV to 78.3 (6.9) % ($P<0.05$ *vs* control as 100%; $n=4$) and 27.0 (4.2) % ($P<0.01$; $n=4$), respectively. After drug washout, $I_{K.tail}$ recovered to 91.7 (3.2) % ($P<0.05$ *vs* propofol 50 μmol litre^{-1}; $n=6$) and 84.6 (4.4) % ($P<0.05$ *vs* thiopentone 100 μmol litre^{-1}; $n=4$), respectively. The normalized activation curves of $I_{K.tail}$ were fitted to the Boltzmann equation (fig. 5). *Vh* was 20.3 (0.2) mV and *s* was 15.6 (0.2) mV in the control ($n=11$). These values remained almost unchanged during administration of drug ($n=11$ for propofol and $n=5$ for thiopentone), except for a slight negative shift by thiopentone 100 μmol litre^{-1}.

Discussion

We have demonstrated that at concentrations of 0.5 μmol litre^{-1} or higher, propofol shortened APD without affecting RMP, and thiopentone had a biphasic effect on APD. Thiopentone 10 μmol litre^{-1} pro-

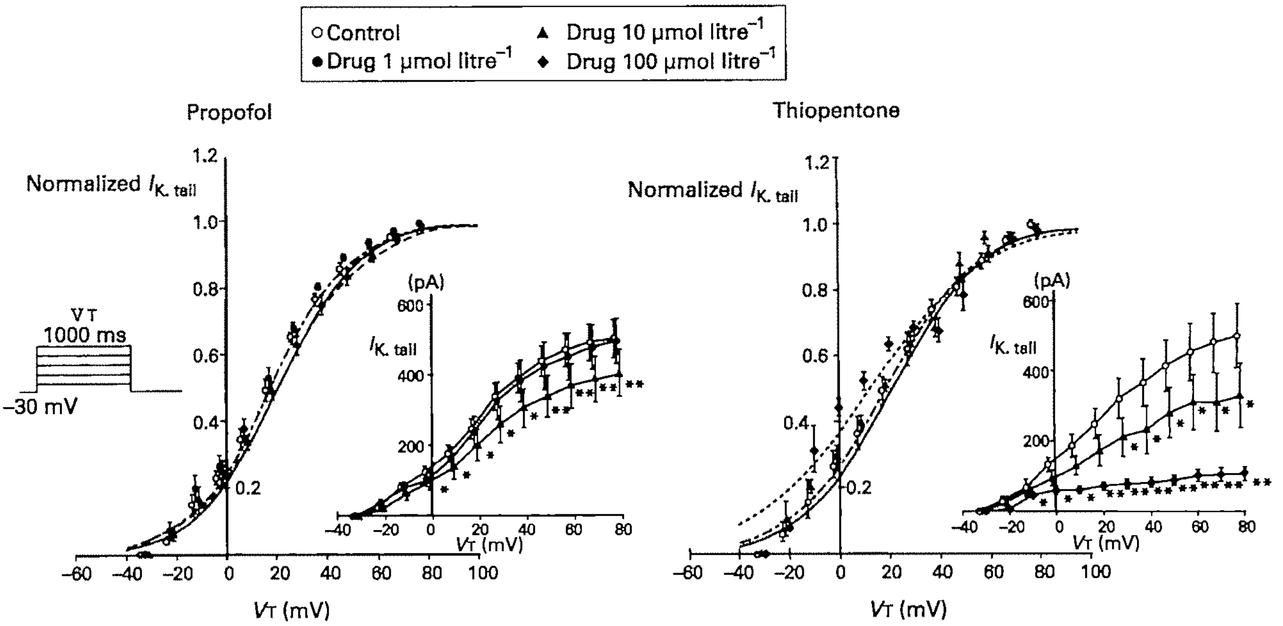

Figure 5 Effects of propofol and thiopentone on activation of I_K. Activation of I_K was initiated using the voltage procedure shown in the inset at the left. I_K was assessed by the tail current amplitude ($I_{K.tail}$). Steady-state activation of $I_{K.tail}$ is plotted on the right side for both propofol and thiopentone. The normalized $I_{K.tail}$ curves were least-square fits of a Boltzmann equation to the mean values of each data group. *$P<0.05$ *vs* control, **$P<0.01$ *vs* control.

longed APD while concentrations higher than 50 μmol litre⁻¹ decreased RMP and abbreviated the prolonged APD to the control level. Propofol at concentration greater than 1 μmol litre⁻¹ suppressed mainly $I_{Ca.L}$ with minimal changes in I_K without affecting I_{K1}. In contrast, thiopentone 10 μmol litre⁻¹ predominantly suppressed I_K with mild suppression of $I_{Ca.L}$ and minimal effects on I_{K1}. At concentrations of 50 μmol litre⁻¹ or higher, thiopentone profoundly depressed $I_{Ca.L}$, I_K and I_{K1}. These results at high concentrations are generally in agreement with previous reports[4 6 9 12 16].

Because the main currents underlying the plateau and repolarization phases of action potentials in guineapig ventricular myocytes are $I_{Ca.L}$, I_K and I_{K1}[19], changes in action potentials can be ascribed mainly to the different potencies of the drugs against these membrane currents. Although at high concentrations propofol suppressed both $I_{Ca.L}$ and I_K[3 12], the main target channel of the drug at lower concentrations has not been clarified. Anaesthetic EC_{50} concentrations of propofol and thiopentone required for lack of response to a painful stimulus are 0.4 μmol litre⁻¹ and 25 μmol litre⁻¹ in free aqueous phases, respectively[20]. The low concentrations used in the our experiments (propofol 1 μmol litre⁻¹ and thiopentone 10 μmol litre⁻¹) correspond approximately to the therapeutic concentrations of the two agents. Our data clearly demonstrated that propofol, at clinically relevant concentrations, predominantly suppressed $I_{Ca.L}$ with minimal or no action on I_K, while thiopentone, at clinically relevant concentrations, was found to exert a preferential action on I_K rather than $I_{Ca.L}$ and I_{K1}.

Barbiturates such as pentobarbitone and thiopentone most likely affect similar parts of the $GABA_A$ receptor, therefore, a confounding effect of a previous pentobarbitone anaesthetic may affect the *in vitro* results of subsequent thiopentone exposure. To the best of our knowledge, however, there has been no report describing the existence of $GABA_A$ receptors in heart tissue. In addition, the effects of pentobarbitone on the cell membrane are not expected to affect the outcome of this study in view of the extensive washing and equilibration periods, including the cell isolation procedures, before the experiments were performed.

The most distinct difference in the membrane actions of the two i.v. anaesthetics was suppression of K^+ currents. Propofol exerted minimal suppression of I_K at low concentrations (1 μmol litre⁻¹) when $I_{Ca.L}$ was depressed, but had no effect on I_{K1}, even at high concentrations (50 μmol litre⁻¹). In contrast, thiopentone significantly suppressed I_K at low concentrations (10 μmol litre⁻¹) with a mild effect on $I_{Ca.L}$, and at high concentrations exhibited strong suppression on I_K with moderate effects on I_{K1}. Concentration-dependent depression of I_{K1} by thiopentone at concentrations greater than 10 μmol litre⁻¹ was also reported in frog atrial and guineapig ventricular myocytes[16]. These may contribute to the different effects of propofol and thiopentone on APD.

Recent studies have highlighted the existence of at least two components of I_K: fast activating I_K ($I_{K.r}$) and slow activating I_K ($I_{K.s}$)[21]. Although we did not examine selective inhibition of the two components of I_K, it is conceivable that propofol and thiopentone have a predominant blocking action on $I_{K.s}$ because of the pulse design (1000 ms depolarization) used and dominant $I_{K.s}$ in guineapig ventricular myocytes[21]. Suppression of I_{K1} induces depolarization of RMP and prolongation of APD. While the latter action may exert prevention of re-entrant arrhythmias because of the long refractory period, similar to class III antiarrhythmic agents, the former induces serious effects on arrhythmogenesis. A decrease in RMP inactivates the fast sodium current ($I_{Na.fast}$) to cause slowing of cardiac impulses. This may facilitate development of re-entry and produce abnormal automaticity. Additionally, depolarization of RMP may account for the negative inotropic effect because it promotes inactivation of $I_{Ca.L}$ under certain conditions. Therefore, thiopentone may be more responsible for the proarrhythmic and negative inotropic actions in ischaemic heart[22].

Three i.v. anaesthetics, ketamine 100 µmol litre^{-1}, methohexitone 100 µmol litre^{-1} and propofol 28 µmol litre^{-1}, have been shown to have different actions on I_{K1} and I_K[12]. Ketamine, thiopentone, etomidate, propofol and midazolam at relatively high concentrations were shown to depress the transient outward K$^+$ current (I_{to}) in canine ventricular myocytes[15 23]. Our study demonstrated that propofol and thiopentone had different selectivity of effects on two voltage-dependent K$^+$ currents. This evidence suggest that i.v. anaesthetics have specific site(s) of actions on the cardiac cell membrane, such as individual ion channels[24] or the lipid environment of the channel, or both, to exert their effects[13], rather than a generalized membrane effect.

Both anaesthetics not only suppressed $I_{Ca.L}$ but also affected current kinetics in a slightly different manner. Although the values of $I_{Ca.L}$ measured included components of "rundown", propofol and thiopentone at clinically relevant concentrations suppressed the peak amplitudes of $I_{Ca.L}$. These results indicate that propofol and thiopentone at anaesthetizing concentrations depress cardiac contractility, at least partly as a result of abbreviation of Ca^{2+}-influx through the sarcolemma. Compared with an equipotent dose of propofol, the decrease in the amount of Ca^{2+} influx produced by thiopentone may be smaller than that produced by propofol in each action potential because of prolonged APD in the former. This observation is compatible with reports that the cardiodepressant effects of propofol are more pronounced and more prolonged than those of equipotent doses of thiopentone when given as a single bolus[25]. This explanation, however, conflicts with most of the previous studies that showed that propofol had little or no effect on cardiac contractility[6 26 27], or was less potent than thiopentone[4 6].

There may be additional factors involved in the modification of Ca^{2+} influx and cardiac contractility by these drugs. During excitation–contraction coupling, Ca^{2+} release from the sarcoplasmic reticulum and trans-sarcolemmal Ca^{2+} entry are two main sources for the Ca^{2+} supply, but the contribution of each component may differ in various species (higher dependence on sarcoplasmic reticulum Ca^{2+}-release in the order of rat>dog, cat>human>guineapig, rabbit>frog ventricle)[28]. Thiopentone[9 11] but not propofol[3 5] has been reported to impair sarcoplasmic reticulum function. In addition, propofol was shown to reduce the second inward current during action potential plateau or depolarizing pulses at positive voltages which was carried presumably by the Na$^+$–Ca^{2+} exchange mechanism[3]. Reduction of this inward current could also be partly attributed to the negative inotropic effect of propofol.

In summary, we found that propofol suppressed mainly $I_{Ca.L}$ with minimal depression of I_K and little or no change in I_{K1}, while thiopentone, at clinically relevant concentrations, demonstrated predominant block of I_K rather than $I_{Ca.L}$ and I_{K1}. The distinct suppressive effects on cardiac function of propofol and thiopentone may result, at least in part, from the different actions on membrane currents forming the repolarization phase of action potentials.

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References

1. Sebel PS, Lowdon JD. Propofol: A new intravenous anesthetic. *Anesthesiology* 1989; 71: 260–277.
2. Hug CC, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, Walawander CA, White PF, Apfelbaum JL, Grasela TH. Hemodynamic effects of propofol: data from over 25,000 patients. *Anesthesia and Analgesia* 1993; 77: S21–S29.
3. Puttick RM, Terrar DA. Effects of propofol and enflurane on action potentials, membrane currents and contraction of guineapig isolated ventricular myocytes. *British Journal of Pharmacology* 1992; 107: 559–565.
4. Park WK, Lynch C III. Propofol and thiopental depression of myocardial contractility: A comparative study of mechanical and electrophysiologic effects in isolated guinea pig ventricular muscle. *Anesthesia and Analgesia* 1992; 74: 395–405.
5. Cook DJ, Housmans PR. Mechanism of the negative inotropic effect of propofol in isolated ferret ventricular myocardium. *Anesthesiology* 1994; 80: 859–871.
6. Azuma M, Matsumura C, Kemmotsu O. Inotropic and electrophysiologic effects of propofol and thiamylal in isolated papillary muscles of the guinea pig and the rat. *Anesthesia and Analgesia* 1993; 77: 557–563.
7. Davies AO, McCans JL. Effects of barbiturate anesthetics and ketamine on the force-frequency relation of cardiac muscle. *European Journal of Pharmacology* 1979; 59: 65–73.
8. Frankl WS, Poole-Wilson PA. Effects of thiopental on tension development, action potential, and exchange of calcium and potassium in rabbit ventricular myocardium. *Journal of Cardiovascular Pharmacology* 1981; 3: 554–565.
9. Housmans PR, Kudsioglu ST, Bingham J. Mechanism of the negative inotropic effect of thiopental in isolated ferret ventricular myocardium. *Anesthesiology* 1995; 82: 436–450.
10. Komai H, Redon D, Rusy BF. Effects of thiopental and halothane on spontaneous contractile activity induced in isolated ventricular muscles of the rabbit. *Acta Anaesthesiologica Scandinavica* 1991; 35: 373–379.
11. Komai H, Rusy BF. Effect of thiopental on Ca^{2+} release from sarcoplasmic reticulum in intact myocardium. *Anesthesiology* 1994; 81: 946–952.
12. Baum VC. Distinctive effects of three intravenous anesthetics on the inward rectifier (I_{K1}) and the delayed rectifier (I_K) potassium currents in myocardium: implications for the mechanism of action. *Anesthesia and Analgesia* 1993; 76: 18–23.
13. Takahashi H, Puttick RM, Terrar DA. The effects of propofol and enflurane on single calcium channel currents of guinea-pig isolated ventricular myocytes. *British Journal of Pharmacology* 1994; 111: 1147–1153.
14. Ikemoto Y. Reduction by thiopental of the slow-channel-mediated action potential of canine papillary muscle. *Pflugers Archiv. European Journal of Physiology* 1977; 372: 285–286.
15. Supan DF, Buljubasic N, Berczi V, Marijic J, Kampine JP, Bosnjak ZJ. Comparative effects of ketamine and thiopental on calcium and potassium currents in isolated canine ventricular cells. *Anesthesiology* 1993; 79: A389.
16. Pancrazio JJ, Frazer MJ, Lynch C III. Barbiturate anesthetics depress the resting K$^+$ conductance of myocardium. *Journal of Pharmacology and Experimental Therapeutics* 1993; 265: 358–365.
17. Hirano Y, Hiraoka M. Barium- induced automatic activity in isolated ventricular myocytes from guinea-pig hearts. *Journal of Physiology (London)* 1988; 395: 455–472.
18. Isenberg G, Klockner U. Calcium tolerant ventricular myocytes prepared by preincubation in a "KB medium". *Pflugers Archiv* 1982; 395: 6–18.
19. Noble D. The surprizing heart: A review of recent progress in cardiac electrophysiology. *Journal of Physiology (London)* 1984; 353: 1–50.
20. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; 367: 607–614.
21. Sanguinetti MC, Jurkiewicz NK. Two components of cardiac delayed rectifier K$^+$ current. *Journal of General Physiology* 1990; 96: 195–215.

22. De Hert SG, Vermeyen KM, Adriaensen HF. Influence of thiopental, etomidate, and propofol on regional myocardial function in the normal and acute ischemic heart segment in dogs. *Anesthesia and Analgesia* 1990; **70**: 600–607.
23. Marijic J, Buljubasic N, Berczi V, Supan DF, Stowe DF, Kampine JP, Bosnjak ZJ. Comparative effects of etomidate, propofol and midazolam on calcium and potassium currents in isolated canine ventricular cells. *Anesthesiology* 1993; **79**: A390.
24. Dilger JP, Vidal AM, Mody HI, Liu Y. Evidence for direct actions of general anesthetics on an ion channel protein. A new look at a unified mechanism of action. *Anesthesiology* 1994; **81**: 431–442.
25. Mulier JP, Wouters PF, Van Aken H, Vermaut G, Vandermeersch E. Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach. *Anesthesia and Analgesia* 1991; **72**: 28–35.
26. Riou B, Besse S, Lecarpentier Y, Viars P. In vitro effects of propofol on rat myocardium. *Anesthesiology* 1992; **76**: 609–616.
27. Ismail EF, Kim SJ, Salem MR, Crystal GJ. Direct effects of propofol on myocardial contractility in *in situ* canine hearts. *Anethesiology* 1992; **77**: 964–972.
28. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: A review of possible mechanisms. *Anesthesiology* 1987; **67**: 745–766.

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Dose–response curve for anaesthetics based on the Monod–Wyman–Changeux model

T. IWAI, H. KIHARA, K. IMAIAND AND M. UCHIDA

Summary

We have analysed the dose–response curve for halothane and isoflurane according to the Monod–Wyman–Changeux (MWC) model. This model describes the nature of the physiological data reported by Wakamori, Ikemoto and Akaike for inhibitory Cl currents induced by GABA or glycine in dissociated rat brain neurones and by Herrington and colleagues for Ca^{2+} currents in clonal pituitary cells. With some assumptions on the difference in response to anaesthetics between patients, the model is applicable *in vivo*, and it also describes well the human dose–response curve for isoflurane reported by Mather, Raftery and Prys-Roberts. However, the steeply sigmoidal dose–response curve in humans for halothane presented by deJong and Eger is difficult to understand with the same model, because it gives rise to unrealistic MWC variables. (*Br. J. Anaesth.* 1996;**77**:517–521)

Key words

Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Model, mathematical.

The mechanism of action of anaesthetics is still controversial. Because the potencies of volatile anaesthetics increase in proportion to their solubility in oil, it has been proposed that general anaesthetics act by disturbing the structure or dynamic properties of the lipid–bilayer portions of nerve membranes. Such perturbations, however, were found to be extremely small at concentrations used clinically. In contrast, physiological studies indicate that specific interactions occur with membrane proteins, such as receptors and ligand-gated ion channels, and these receptors have been proposed as sites of anaesthetic action[1,2]. For example, the γ-aminobutyric acid (GABA) receptor is very sensitive to most volatile anaesthetics; inhalation agents, halothane and enflurane, at surgical concentrations, markedly enhanced inhibitory currents induced by GABA, causing a shift in the dose–response curve (response of current to GABA concentration) to lower GABA concentrations[3]. Moss, Franks and Lieb demonstrated that the activity of a soluble lipid-free enzyme, firefly luciferase, was inhibited by a range of anaesthetics at concentrations close to their respective EC_{50} values[4]. Some agents with optical isomers show stereoselectivity[5]. This suggests that anaesthetics may act by binding directly to proteins.

Changeux has reviewed the most thorough study on the nicotinic acetylcholine receptor, and demonstrated the allosteric nature of ligand-gated ion channels[6]. The dose–response curve determined experimentally suggests binding of anaesthetic molecules to a receptor protein molecule. In this article, we have analysed the behaviour of anaesthetics in the framework of the Monod–Wyman–Changeux (MWC) model[7], which has been used successfully to understand the behaviour of allosteric protein molecules[8–10]. We refer to the electrophysiological data reported by Wakamori, Ikemoto and Akaike[3] and by Herrington and colleagues[11] to see how well the MWC model works. We then analyse the data on anaesthetic potency for humans presented by deJong and Eger[12] and by Mather, Raftery and Prys-Roberts[13] on the basis of the MWC model.

Methods

IN VITRO DOSE–RESPONSE

According to the MWC model[7], we assume that a receptor protein molecule has two different conformations, R and T, each of which contains r binding sites for a ligand X; the sites are similar and independent. The whole system is assumed to be in equilibrium. The R form is termed anaesthetic-sensitive, because anaesthetic molecules (the ligand) bind more readily to the R form of the receptor molecule than to the T form. The binding equilibrium constant K_T for a site on the T-form molecules is usually much smaller than that for the R-form molecules, K_R, so that the ratio c $(=K_T/K_R)$ is much smaller than unity. However, in the absence of anaesthetic ($[X]=0$), most of the receptor molecules are in the T form; the equilibrium constant for the $R \rightleftharpoons T$ transition, $L(=[T]/[R])$, is usually much greater than unity. Hence there is near-zero response at low concentrations of ligand. As the concentration of ligand increases, the ligand binds mainly to the R-form molecules giving combined molecules RX, RX_2, RX_3, as one, two and three of the receptor sites on the R-form molecules become occupied with ligand X. In addition, there are some TX, TX_2, TX_3, molecules, and the numbers of the RX_i molecules is

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equal to that of the TX_i molecules (i =0, 1, 2,..., r) at the ligand concentration giving 50% response. Eventually, at high concentrations of X, almost all the receptor molecules are in the RX_i form and the response is maximal. At all concentrations of X, the response, expressed as a fraction Z of the maximum, is considered to be equal to the amount of RX_i molecules as a fraction of the total RX_i and TX_i molecules. The MWC formulation (appendix) gives the fractional response Z as follows:

$$Z = \frac{(1+K_Rx)^r}{(1+K_Rx)^r+L(1+cK_Rx)^r} \qquad (1)$$

where x=ligand concentration at receptor sites: x =[X]. The MWC variables of the equilibrium process, K_R, c, L and the number of sites r, should be determined from reasonable fitting to the experimental dose–response data.

In practice, we determined those variables using the Hill approximation. The experimental dose–response curve is conventionally expressed by:

$$y = \frac{x^n}{x_m^n+x^n} \qquad (2)$$

where n=the Hill coefficient and is a measure of cooperativity (n >1 is the condition of cooperativity). When n is large, the curve shows high cooperativity and is steep in shape. Constant x_m is the x value at a half-maximal point (y=50%). The Hill coefficient n can be determined from the Hill plot, $\ln[y/(1-y)]$ *vs* $\ln x$, in which the slope at $x=x_m$ gives the n value. Starting from those values estimated graphically, we determined the Hill variables, n and x_m, using the least-square fitting of equation (2) to the data points.

According to Colosimo, Brunori and Wyman[14], if the experimental dose–response curve is symmetrical with respect to the half-maximal point $x=x_m$, it follows that:

$$L=c^{-1/2} \text{ (symmetrical condition)} \qquad (3)$$

and

$$K_Rx_m = c^{-1/2} \text{ and } n = \frac{1-c}{(1+\sqrt{c})^2}r \qquad (4)$$

We assumed some integer for r (larger than the Hill coefficient n) at first and then obtained other variables from equations (3) and (4). We attempted to determine the final r value for which the MWC curve, $Z=Z(x)$, fits best to the experimental one through trials with different r values.

IN VIVO DOSE–RESPONSE

The basis of a clinical dose–response curve is essentially different from that of an *in vitro*, dose–response curve, because the clinical curve is based on statistics of the logit or probit model. Thus we cannot apply the MWC model to the *in vivo* case by itself. We assume, however, that some log-normal distribution of the *in vivo* curve, instead of a delta function, against anaesthetic concentration is caused by the difference between individual patients in threshold concentrations required for not responding to surgical incision. First, we assume that all individuals have the same receptor molecules in sufficient concentrations to respond. Second, we assume that such thresholds are determined by fractions of active combined molecules RX_i to the total TX_i and RX_i molecules. In other words, we assume that anaesthetic-sensitive patients do not respond to surgical incision even at low fractions, while non-sensitive patients still respond at high fractions. Using this assumption the dose–response curve derived from our MWC model is consistent with statistics of the univariate binary model. Third, we assume that the anaesthetic concentration is the same as the ligand concentration at receptor sites. Based on these assumptions we apply the MWC model to analyse *in vivo* and *in vitro* dose–response data. We consider that the fractional response Z in equation (1) is the percentage of patients not responding to anaesthetics and x is the anaesthetic concentration.

Results

IN VITRO DOSE–RESPONSE

As an example of a ligand–receptor system, we referred to the electrophysiological results of Wakamori, Ikemoto and Akaike in dissociated CNS neurones of the rat[3], and examined the MWC model in the following cases: normalized response of the Cl^- current evoked by GABA 3×10^{-6} mol litre^{-1} and glycine 2×10^{-5} mol litre^{-1} as a function of halothane concentration x. We determined the Hill variables as follows: n=1.8 and x_m=0.21 mmol litre^{-1} for GABA; n=1.9 and x_m=0.37 mmol litre^{-1} for glycine. These half-maximal concentrations are comparable with clinical concentrations; MAC of halothane is 0.75%atm, which gives a concentration of 0.24 mmol litre^{-1} in the water phase at 37 °C. We then evaluated the three variables in the MWC model using equations (3) and (4) for several r values for GABA (fig. 1) and for glycine (fig. 2). In both cases, the MWC curves described well the sigmoidal nature of the experimental dose–response curves, but we could not definitively determine the r values. As seen in reference[9], more data points are necessary to determine exactly the number of sites r. Among those MWC curves, that for r=2 agreed with its respective Hill curve, and the error sum of squares was smaller for r=2 than for the others in both cases. From these we set r=2 for both cases, and the MWC variables for r =2 and the related Hill variables are listed in table 1.

We also examined the MWC model for the effect of halothane on the high-threshold component Ca^{2+} current of clonal (GH_3) pituitary cells reported by Herrington and colleagues[11], as an example of ion channels. The Hill variables were determined as n=1.6 and x_m=0.84 mmol litre^{-1}. It is noted that the half-maximal concentration x_m is three or four times larger than the clinical concentration. Figure 3 shows our MWC curves for various r values and their data points. Here we also failed to determine definitively the r value, but the cooperative nature of the experimental curve was expressed well by the MWC model and the Hill approximation. As seen in figure 3, the MWC curve for r=2 is close to the Hill curve, and the error sum of squares is smaller than for the others. For the same reasons as mentioned above, we set r=2, and the MWC variables are listed in table 1.

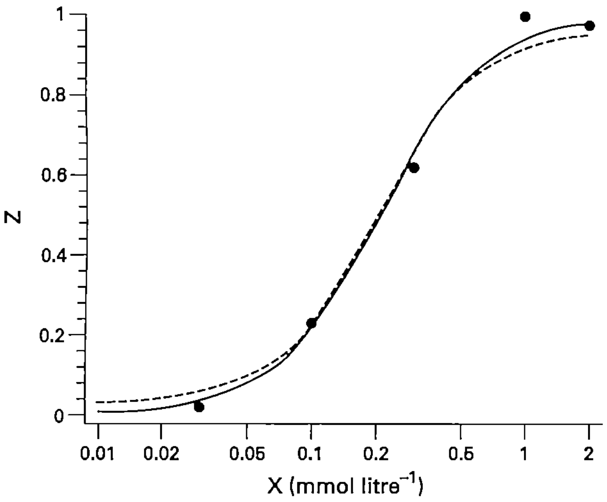


Figure 1 Response relationship of GABA-induced Cl⁻ current to halothane concentration. The solid curve was obtained from the MWC calculation for r=2; the curve of the Hill approximation, n=1.8 and x_m=0.21 mmol litre^{-1}, is on the same solid curve. The broken curves are those for r=4, 8 and 10, which agree with each other within the limit of errors. Data points were read from[3]; the response was normalized to the peak current induced by GABA 3×10^{-6} mmol litre^{-1} alone.

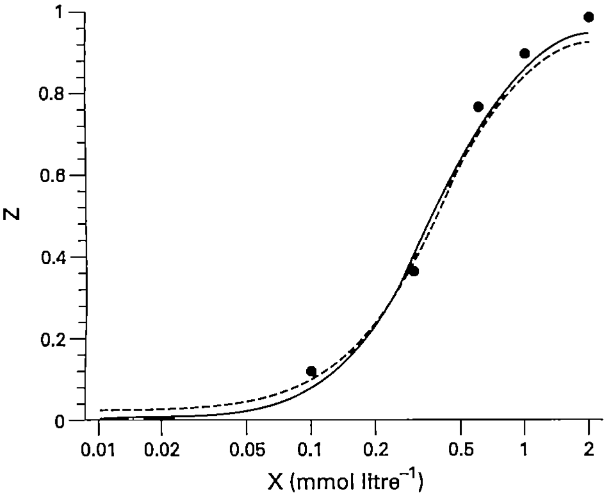


Figure 2 Response relationship of glycine-induced Cl⁻ current to halothane concentration. The solid curve was obtained from the MWC calculation for r=2; the curve obtained from the Hill approximation, n=1.9 and x_m =0.37 mmol litre^{-1}, is on the same one. The broken curves are those for r=4, 8 and 10, which agree with each other within the limit of errors. Data points were read from[3]; response was normalized to the peak current induced by glycine 2×10^{-5} mmol litre^{-1} alone.

IN VIVO DOSE–RESPONSE

Anaesthetic dose–response data in humans were reported by deJong and Eger for halothane[12], and by Mather, Raftery and Prys-Roberts for isoflurane[13]. For halothane, figure 4 shows the Hill curves for various n values, where x_m=0.75 %atm =0.24 mmol litre^{-1}, together with the data points[12]. The least-square fitting of equation (2) gave x_m=0.24 mmol litre^{-1} and n=27, which is much larger than n<2 for the *in vitro* results mentioned above. In this case, it was not possible to determine the number of binding sites and it is only possible to note that the r value is an integer more than 27 (see equation (4)). Our trials for r=28, 30 and 40 gave MWC curves which agreed with each other and with the Hill curve for n=27. The MWC variables for r=30 are listed in table 1 as an example. Notice that the L value is of the order of magnitude of 10^{38} which is unrealistically large.

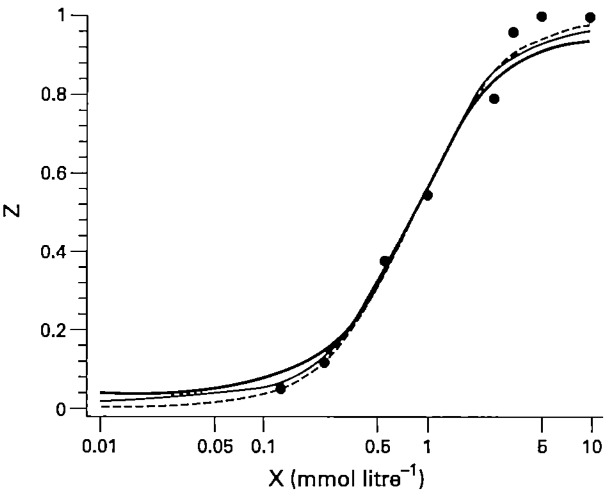


Figure 3 Concentration dependence of block of Ca^{2+} current by halothane. The solid single curve was obtained from the MWC calculation for r=2, the solid heavy curve for r=4, 8 and 10 and the broken curve is the Hill approximation: n=1.6 and x_m=0.84 mmol litre^{-1}. Data points were read from[11].

Table 1 Hill variables n and x_m, and MWC variables K_R, K_T, c and L, and the number of binding sites r. A was determined from[3] for GABA-induced Cl⁻ current (fig. 1); B from[3] for glycine-induced Cl⁻ current (fig. 2); C from[11] for Ca^{2+} current (fig. 3); D from[12] for humans (fig. 4); and E from[14] for humans (fig. 5). A to D halothane, E = isoflurane

	n	r	x_m (mmol litre^{-1})	K_R (mmol litre^{-1})	K_T (mmol litre^{-1})	c	L
A	1.8	2	0.21	90	0.25	2.8×10^{-3}	360
B	1.9	2	0.37	105	0.069	6.6×10^{-1}	1520
C	1.6	2	0.84	11	0.13	1.2×10^{-2}	81
D	27	30	0.24 %atm	79 (%atm)$^{-1}$	0.22 (%atm)$^{-1}$	2.8×10^{-3}	2.3×10^{38}
E	3.6	4	1.03	18	0.052	2.8×10^{-3}	1.3×10^{5}

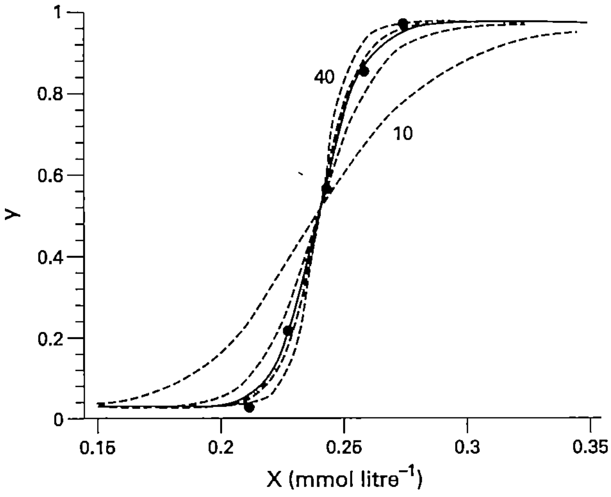


Figure 4 Anaesthetic potency of halothane in humans. All curves are obtained from the Hill approximation. The solid curve is for n=27 and agrees with the MWC curve for r=30; the four broken curves are for n=10, 20, 30 and 40 in order of steepness, of which the n values of 10 and 40 are indicated. x_m=0.24 mmol litre^{-1}=0.75 %atm. Data points were referred to[12].

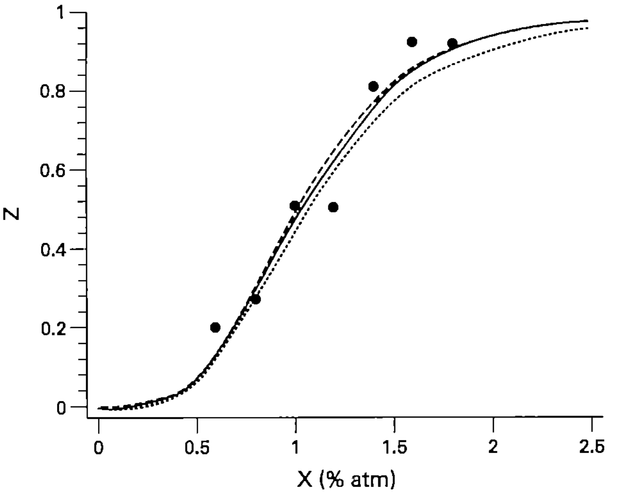


Figure 5 Anaesthetic potency of isoflurane in humans. The solid curve was obtained from the MWC calculation for r=4; the Hill approximation, n=3.6 and x_m=1.03%atm, is on the same solid curve. The broken curves (- - - and ⋯) are for r=8 and r=12, respectively. Data points were referred to[13].

In contrast, the *in vivo* dose–response curve exhibited a much lesser slope for isoflurane. A least-square fitting of the data points[13] to equation (2) gave the Hill variables as n=3.6 and x_m=1.03 %atm. Figure 5 shows the data points and our MWC curve for three r values. The MWC curve for r=4 gave the smallest error sum of squares among the trials with various r values. The MWC variables for r=4 and the Hill variables are listed in table 1.

Discussion

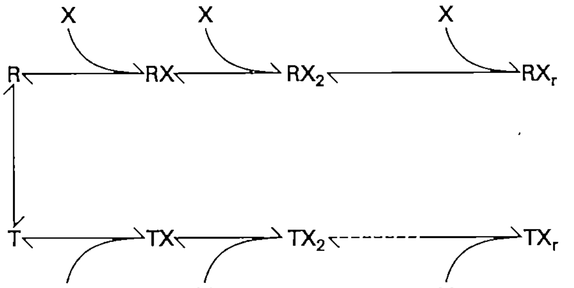
The MWC model describes the nature of the dose–response curve in the electrophysiological experiments for halothane, although the number of binding sites r cannot be determined strictly as yet. If we assume that the fractional response is the percentage of patients not responding to anaesthetics, the MWC model also describes the sigmoidal nature of the clinical dose–response curve for isoflurane. In contrast, the human dose–response curve for halothane is difficult to understand on the basis of the MWC model because of the extremely large value of L.

Mather, Raftery and Prys-Roberts[13] suggested that the steepness of the human dose–response curve obtained by deJong and Eger[12] was apparently enhanced because their sampling method tended to exclude low and high concentrations. For example, the Hill coefficient n, which is a measure of steepness, can be estimated to be 3.6[13] or 8.4[12] for isoflurane. If we assume that such a difference is true proportionally for another anaesthetic, the n value would be reduced from 27 to approximately 10 for halothane. However, it seems that the *in vivo* curve is steeper than the *in vitro* curve.

Our *in vivo* dose–response curve must be governed by the statistics of a univariate binary model on our assumptions. However, its distribution may not agree with the log-normal distribution. In order to check the difference between our distribution and log-normal distribution, we estimated EC_{50} and EC_{95} values for isoflurane from our curve. The values obtained were 1.03%atm and 2.36%atm, respectively, which are in agreement with those of Mather, Raftery and Prys-Roberts (EC_{50}=1.00%atm and EC_{95}=2.16%atm)[13].

Appendix

As mentioned in the text, the MWC model assumes that a receptor molecule has two conformations, R and T, and each form contains r binding sites for a ligand X. The equilibrium scheme of the ligand–receptor system is as follows:



Taking into account the probability factors for the binding of the R and T forms to receptor molecules, we have the following equilibrium equations:

$$[\mathrm{T}]=L\,[\mathrm{R}],$$

$$[\mathrm{RX}]=r\,K_{\mathrm{R}}\,x[\mathrm{R}],\qquad [\mathrm{TX}]=r\,K_{\mathrm{T}}\,x[\mathrm{T}],$$

$$[\mathrm{RX}_2]=(r\,(r-1)/2!)\,K_{\mathrm{R}}{}^2\,x^2[\mathrm{R}],\ [\mathrm{TX}_2]=(r\,(r-1)/2!)\,\mathrm{K}_{\mathrm{T}}{}^2\,x^2[\mathrm{T}],$$

$$[\mathrm{RX}_i]=(r\,!/i\,!(r-i\,)!)\,K_{\mathrm{R}}i\,x^i[\mathrm{R}],\ [\mathrm{TX}_i]=(r\,!/i\,!(r-i\,)!)\,K_{\mathrm{T}}{}^i\,x^i\,[\mathrm{T}],$$

$$[\mathrm{RX}_r]=K_{\mathrm{R}}{}^r\,x^r[\mathrm{R}],\ [\mathrm{TX}_r]=K_{\mathrm{T}}r\,x^r[\mathrm{T}],$$

where x=concentration of ligand X, and K_{R} and K_{T}=binding equilibrium constants for a site in the R form and T form, respectively. Then the concentration of the R-form molecules, which is sometimes called the R state, is given by:

$$[\mathrm{R}]+[\mathrm{RX}]+[\mathrm{RX}_2]+\ldots+[\mathrm{RX}_r]=(1+K_{\mathrm{R}}\,x\,)^r\,[\mathrm{R}],$$

and that of the T-form molecules, the T state, is given by:

$$[\mathrm{T}]+[\mathrm{TX}]+[\mathrm{TX}_2]+\ldots+[\mathrm{TX}_r]=(1+K_{\mathrm{T}}x)^r[\mathrm{T}]=L\,(1+c\,K_{\mathrm{R}}\,x\,)^r[\mathrm{R}].$$

Therefore, the fraction of the R-form molecules to the total R-form and T-form molecules is expressed by:

$$Z=\frac{(1+K_Rx)^r}{(1+K_Rx)^r+L(1+cK_Rx)^r} \qquad (1)$$

Equation (1) is defined as the state function[6 7]. r≥2 is the necessary condition of cooperativity, and cooperativity is marked when L is much greater than 1.

References

1. Dluzewski AR, Halsay MJ, Simmonds AC. Membrane interactions with general and local anaesthetics: a review of molecular hypotheses of anaesthesia. *Molecular Aspects of Medicine* 1983; **6**: 459–573.
2. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; **367**: 607–614.
3. Wakamori M, Ikemoto Y, Akaike N. Effects of two volatile anesthetics and a volatile convulsant on the excitatory and inhibitory amino acid response in dissociated CNS neurons of the rat. *Journal of Neurophysiology* 1991; **66**: 2014–2021.
4. Moss GWJ, Franks NP, Lieb WR. Modulation of the general anesthetic sensitivity of a protein: a transition between two forms of firefly luciferase. *Proceeding of the National Academy of Science USA* 1991; **88**: 134–138.
5. Jones MV, Harrison NL. Effects of volatile anesthetics on the kinetics of inhibitory postsynaptic currents in cultured rat hippocampal neurons. *Journal of Neurophysiology* 1993; **70**: 1339–1349.
6. Changeux J-P. Functional architecture and dynamics of the nicotine acetylecholine receptor: an allosteric ligand-gated ion channel. *Fidia Research Neuroscience Award Lectures* 1990; **4**: 21–168.

7. Monod J, Wyman J, Changeux J-P. On the nature of allosteric transitions: a plausible model. *Journal of Molecular Biology* 1965; **12**: 88–118.
8. Shulman RG, Hopfield JJ, Ogawa S. Allosteric interpretation of haemoglobin properties. *Quarterly Review of Biophysics* 1975; **8**: 325–420.
9. Imai K, Yoshikawa S, Fushitani K, Takizawa H, Handa T, Kihara H. Inference of allosteric unit in chlorocruorin, erythrocruorin, and hemerythrin on the basis of the Monod–Wyman–Changeux model. In: Linzen B, eds. *Invertebrate Oxygen Carriers*. Berlin: Heidelberg, 1986; 367–374.
10. Tsuruta H, Vachette P, Sano T, Moody MF, Amemiya Y, Wakabayashi K, Kihara H. Kinetics of the quaternary structure change of aspartate transcarbamylase triggered by succinate, a competitive inhibitor. *Biochemistry* 1994; **33**: 10007–10012.
11. Herrington J, Stern RC, Evers AS, Lingle CJ. Halothane inhibits two components of calcium current in clonal (GH_3) pituitary cells. *Journal of Neuroscience* 1991; **11**: 2226–2240.
12. deJong RH, Eger EI. MAC expanded: AD_{50} and AD_{95} values of common inhalation anesthetics in man. *Anesthesiology* 1975; **42**: 384–389.
13. Mather C, Raftery S, Prys-Roberts C. Somatic movement and oesophageal motility during isoflurane anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 40–44.
14. Colosimo A, Brunori M, Wyman J. Concerted changes in an allosteric macromolecule. *Biophysical Chemistry* 1974; **2**: 338–344.

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Visual evoked potentials and nitrous oxide-induced neuronal depression: role for benzodiazepine receptors

M. DZOLJIC, W. ERDMANN AND M. R. DZOLJIC

Summary

We have examined the role of benzodiazepine receptors in nitrous oxide-induced neuronal depression in rats. The changes in neuronal excitability induced by nitrous oxide and the benzodiazepine inverse agonist, Ro15-4513, were monitored by measurement of visual evoked potentials (VEP). Administration of Ro15-4513 10 mg kg^{-1} i.p., in rats breathing air, did not affect the amplitude or latency of VEP. However, the same concentrations of Ro15-4513 antagonized nitrous oxide-induced depression of VEP amplitudes. We conclude that antagonism of nitrous oxide-induced depression by Ro15-4513 indicates that at least part of the decreased neuronal excitability caused by nitrous oxide could be ascribed to interactions with the GABA$_A$ receptor complex. (*Br. J. Anaesth.* 1996;**77**:522–525)

Key words

Anaesthetics gases, nitrous oxide. Hypnotics benzodiazepine, Ro15-4513. Monitoring, evoked potentials. Receptors, amino acid. Rat.

The high correlation between the degree of lipophilicity and potency of anaesthetic agents, ranging from inert gases such as xenon to alcohols of varying length, has always been interpreted as evidence that general anaesthesia occurs secondary to non-specific disruption of lipids of neuronal cell membranes[1]. Although the solubility relationships provide a framework for any proposed theory of anaesthesia, the mechanism of action of anaesthetics and corresponding membrane disturbances remain intriguing. Recent studies have focused on membrane proteins as a site of anaesthetic action[2 3]. In this respect two transmitter receptors, namely glutamate[4] and γ-aminobutyric acid (GABA)[5], were considered frequently as mediators of anaesthetic drugs.

GABA is the major inhibitory neurotransmitter in the mammalian brain and thus a prime candidate for a mechanism of the depressant effects of anaesthetic agents. The increase in Cl$^-$ conductance caused by GABA can be modulated by benzodiazepines[6], ethanol[7] and various inhalation anaesthetics[5]. Galindo[8] showed that halothane potentiated the inhibitory action of GABA in the cuneate nucleus. These results have been confirmed recently by Jones, Brooks and Harrison[5], who showed enhancement of GABA-activated Cl$^-$ currents in cultured rat hippocampal neurones by enflurane, halothane and isoflurane.

Glutamate-activated receptors are other obvious targets for general anaesthetics. The NMDA receptor, when activated, causes a Ca^{2+} influx modulating the excitability of a neurone. Ethanol-reduced, NMDA-induced Ca^{2+} currents in cultured hippocampal neurones[9] share this property with other general anaesthetics[10]. As many ion channels have been shown to be affected differently by anaesthetics[11–13], it appears that an interaction between a particular channel and an anaesthetic cannot provide a basis for a general mechanism of anaesthesia. Ethanol, for example, potentiates GABA binding and inhibits NMDA receptors, making more pathways possible for the clinically observed effects. An imidazobenzodiazepine inverse agonist, Ro15-4513 (ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo [1,5α] [1,4] benzodiazepine-3-carboxylate) however, selectively blocks ethanol-stimulated Cl$^-$ uptake[14] and many of the behavioural effects[15 16].

Mice rendered tolerant to nitrous oxide also exhibit cross-tolerance to ethanol hypnosis[17], suggesting a similarity in mode of action between these two drugs. This study was undertaken to see if nitrous oxide-induced neuronal depression can be altered by a benzodiazepine inverse agonist. Changes in neuronal excitability induced by nitrous oxide and Ro15-4513 were measured in this study by visual evoked potentials (VEP). This method was used previously for monitoring the central effects of nitrous oxide in humans[18] and animals[19 20]. All of these studies showed that VEP is a reliable method for measurement of nitrous oxide-induced neuronal depression.

Materials and methods

We used male adult albino Wistar rats, weighing 250–300 g. Each rat was placed in a separate cage

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and provided with food and water *ad libitum*. The holding room was maintained at approximately 22°C, 50% humidity and a 12-h light–dark cycle (light on at 08:00). The animals were allowed at least 7 days for adaptation to these circumstances before surgery. Before electrode placement, the rats were anaesthetized with Hypnorme 0.15 ml 100 g^{-1} (Hypnorme=fluanison 10 mg and fentanyl 0.2 mg ml^{-1}).

Individual stainless steel screw electrodes were implanted surgically over the right and left visual cortices at points 7 mm posterior to the bregma and 3 mm lateral to the midline. A reference electrode was placed in the frontal sinus. The electrodes were soldered to a miniature socket, which was fixed to the skull with dental cement. After a 7-day postoperative recovery period, each rat was habituated to the recording procedure. The experiments and habituation were performed with rats moving freely and housed in an exposure chamber which was maintained at a temperature of 22 °C. The exposure chamber was made of glass surrounded on all sides by mirrors except for the top where the flash-lamp was placed. This allowed complete illumination of the exposure chamber in all directions. During habituation, the electrode leads were connected and a flash stimulus was induced once every 7 s for 10 min. Such treatment was repeated daily over the following 3–4 days, until VEP discharges stabilized. Previous studies have shown that under these conditions, VEP discharges stabilize after several days[21]. During the experiments the flashlight was triggered by a Grass S44 stimulator at a frequency of 0.14 Hz. Brain responses were amplified with a Grass model 79 B, connected to an analogue-to-digital converter (Lab Master, Scientific solutions Inc., OH, USA), which was triggered by the Grass S44 stimulator after every flashlight. A computer connected to the analogue-to-digital converter performed the averaging of 25 VEP over an 800-ms epoch after every flashlight and printed the results. Potentials less than −500 µV or more than +500 µV were defined as artefacts induced by movement and rejected automatically. With a few rejections per measurement a typical recording of one averaged VEP lasted for approximately 3 min. VEP discharges were recorded in animals breathing air before exposure to 70% nitrous oxide–30% oxygen.

A concentration of 70% nitrous oxide was selected because in many studies of nitrous oxide-induced dependence phenomena in animals[22] or nitrous oxide-induced changes in evoked potentials in humans[23], the same or a similar concentration of nitrous oxide was used. In addition, a concentration of 70% nitrous oxide is used frequently during clinical anaesthesia. While exposed to nitrous oxide for 60 min, i.p. administration of drug (Ro15-4513 10 mg kg^{-1}) or vehicle (Tween 0.3%, volume 1 ml) was given. VEP were measured at intervals of 15 min for the following 45 min. During the recording session the animal was observed closely to ensure that recording was performed while the eyes were open. The flashlight itself was usually enough to alert the animal. Nitrous oxide, oxygen and carbon dioxide were monitored during the experiment with a Datex Capnomac Ultima (Datex Instrumentarium Corp., Helsinki, Finland). Nitrous oxide was withdrawn by exposing the animals to air. Tween was obtained from Sigma Chemical Co (St Louis, MO, USA) while Ro15-4513 was obtained from Hoffmann-La Roche. A VEP during the first 500 ms normally includes three positive–negative component complexes. Peak-to-peak amplitudes and peak latency were determined. Peak-to-peak amplitudes obtained during exposure to nitrous oxide were compared with values recorded while the rats were breathing air. Data are presented as mean (SEM); *n*=number of animals tested. Significance of differences in mean values was examined by analysis of variance (ANOVA) (P<0.05).

Results

An example of a visual evoked potential response in one rat, in air, is shown in figure 1. The typical evoked potential is characterized by six waves, labelled P1 to N3. As the baseline may vary throughout the experiment we looked at top-to-top amplitudes. Although all top-to-top amplitudes showed a decrease when the rat was exposed to nitrous oxide[20], only potentials with a latency of 100 ms or more were studied because of their stability. Therefore, only amplitudes P2-N2, N2-P3 and P3-N3 were studied.

To asses the effects of Ro15-4513 without the interference of nitrous oxide, a group of eight rats, while breathing air, was given Ro15-4513 10 mg kg^{-1} in 0.3% Tween i.p. Top-to-top amplitudes are shown in figure 2. After obtaining control measurements, an i.p. injection was given (arrow in fig. 2) and the first

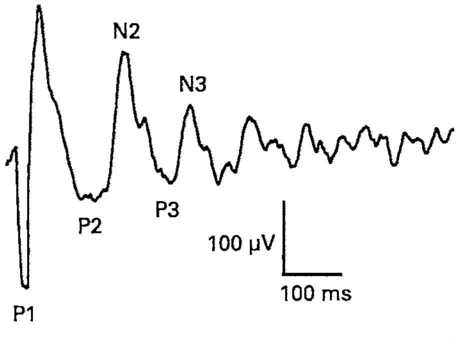

Figure 1 An example of a visual evoked potential (VEP) in one rat while the animal was breathing air. Amplitude peaks are marked P1 to N3.

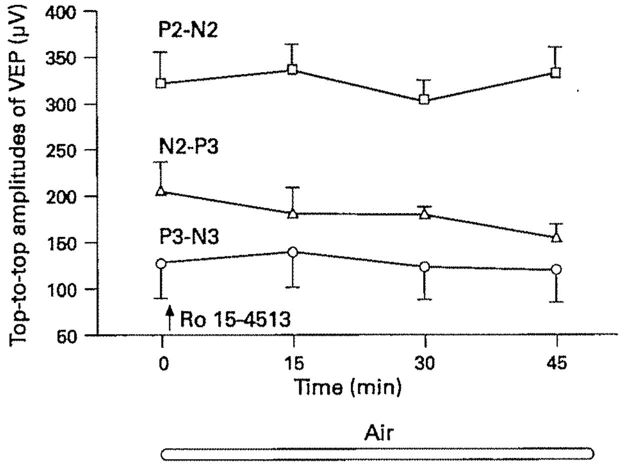

Figure 2 Top-to-top values P2-N2 (□), N2-P3 (△) and P3-N3 (○) were not influenced by injection of Ro15-4513 10 mg kg^{-1} (arrow) while the animals breathed air (*n*=8).

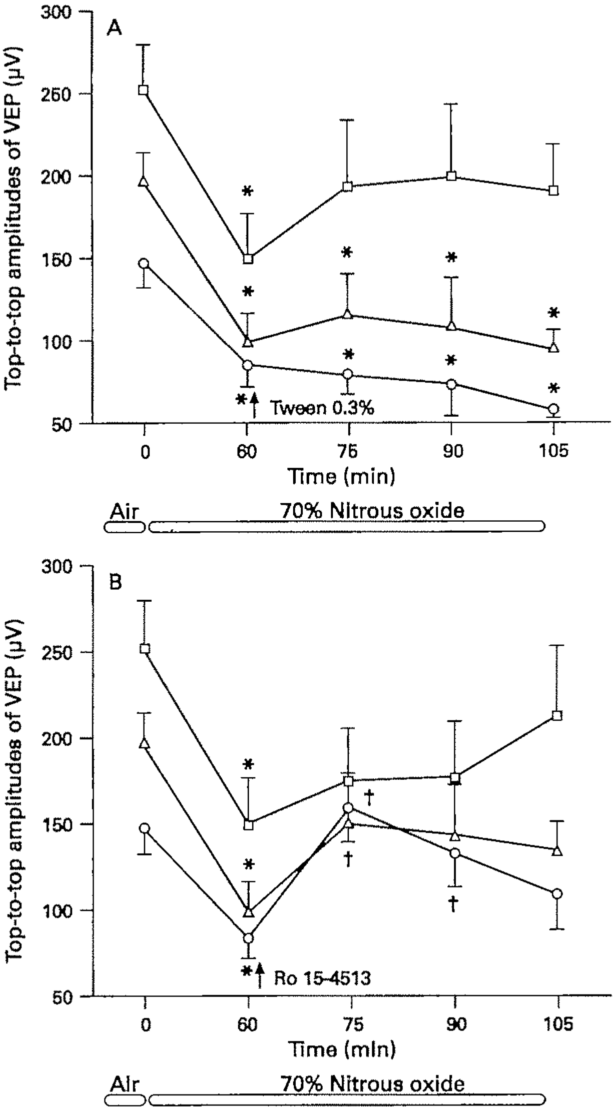

Figure 3 Peak-to-peak amplitude values of VEP (P2-N2 (□), N2-P3 (△) and P3-N3 (○)) in rats (n=20) during exposure to air and 70% nitrous oxide. A: Amplitude values after injection (arrow) with the solvent Tween while animals were breathing nitrous oxide (n=10). Note that N2-P3 and P3-N3 did not recover to normal values while P2-N2 showed a tendency towards recovery. B: Normalization of amplitude values towards those obtained during exposure to air after injection of Ro15-4513 (n=10). *P<0.05 compared with initial values obtained in air; †P<0.05 compared with values obtained after 60 min exposure to nitrous oxide.

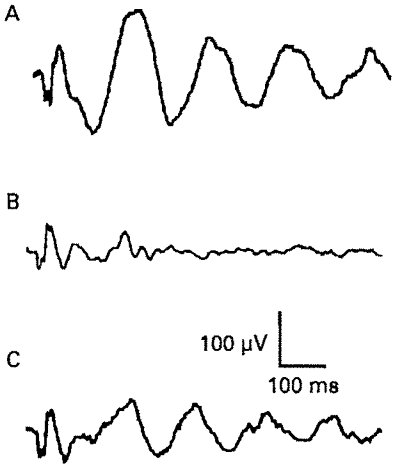

Figure 4 Three VEP measurements in one rat. A: VEP during breathing air. This is an example of a normal VEP after some training of the animal and habituation to the flashlight. B: VEP measured while the animal was breathing 70% nitrous oxide in oxygen (note marked depression of amplitudes with a long latency). C: VEP measured while the animal was exposed to nitrous oxide but 15 min after injection of Ro15-4513.

VEP after injection was measured 15 min later. No significant changes in top-to-top amplitudes were observed within 45 min after administration of Ro15-4513 and no change in general behaviour was observed.

Figure 3A and 3B depicts top-to-top amplitudes of 20 rats showing an expected depression of all three amplitudes after 60 min of exposure to nitrous oxide compared with values obtained in air (control values)[20]. While breathing nitrous oxide, 10 animals were given the solvent 0.3% Tween 1 ml i.p. (arrow in fig. 3A) while others received Ro15-4513 (fig. 3B). In the following 45 min VEP were measured at 15-min intervals in both groups. Animals given Tween showed no normalization of amplitudes towards values obtained in air, except for P2-N2. As this top-to-top amplitude proved to be sensitive to handling or i.p. injection of solvent, or both, it was not evaluated further. After administration of Ro15-4513, however, top-to-top values for N2-P3 and P3-N3 increased significantly compared with values obtained after 60 min exposure to nitrous oxide. Additionally, all observed amplitudes recovered to values that were not significantly different from baseline. Administration of nitrous oxide and i.p. injection of the solvent Tween or Ro15-4513 had no influence on latency (not shown).

Figure 4 shows examples of three VEP measurements in one rat. The first VEP (fig. 4A) was measured while the animal was breathing air. Pronounced depression of the VEP amplitudes could be observed when rats were exposed to nitrous oxide (fig. 4B). The last VEP (fig. 4C), was measured in the same animal, still breathing nitrous oxide, but 15 min after i.p. injection of Ro15-4513 10 mg kg^{-1}.

An additional observation was that after injection of Ro15-4513, animals showed increased activity caused by rotational behaviour, which did not occur in rats while breathing air but was common in rats exposed to nitrous oxide. Therefore, although aroused, the animals did not behave normally until exposure to nitrous oxide was discontinued.

Discussion

The mechanism of action of inhalation anaesthetic agents remains obscure, although there is substantial evidence that at least part of the effects may be explained by potentiation of the GABAergic system[5,24]. The role of the GABAergic system on the effects produced by inhalation of nitrous oxide has, to our knowledge, never been explored. When involvement of the GABAergic system is investigated, and particularly when the benzodiazepine site of the GABA receptor complex is of interest, a benzodiazepine antagonist or inverse agonist, or both, may be used. Using an antagonist such as flumazenil (Ro15-1788) may give results easier to interpret compared with inverse agonists. Unfortunately, flumazenil has some intrinsic activities. This drug decreased the minimum alveolar concentration of isoflurane in dogs when given i.v., suggesting partial agonist activity[25]. In addition, flumazenil was unable to alter methoxyflurane-induced sleep time in mice, but antagonized the reduction in sleep time produced by Ro15-4513[26]. This combined with unfavourable pharmacokinetics[27] made a study with flumazenil, in freely moving rats, unsuitable. Our control experiments showed that Ro15-4513 did not have any effect on the VEP when given at a concentration of 10 mg kg^{-1} (fig. 2). The same concentration of Ro15 4513, however, reversed the changes in VEP induced by nitrous oxide (fig. 3B). The fact that the animals persisted in their unusual rotational behaviour suggests that this reversal in nitrous oxide-induced anaesthesia was only partial, although with regard to VEP, complete reversal was obtained. Higher concentrations of Ro15-4513 may have produced further improvement towards normal behaviour but would make interpretation less obvious as higher concentrations have epileptogenic properties.

In summary, our results indicated that neuronal depression induced by nitrous oxide was sensitive to antagonism by Ro15-4513. In this respect nitrous oxide resembles alcohol and other inhalation anaesthetics. Although the precise interaction between nitrous oxide and the GABA receptor is not clear, our results indicate that at least part of the decreased neuronal excitability caused by nitrous oxide could be ascribed to interactions with a binding site on the $GABA_A$ receptor complex.

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References

1. Miller KW, Paton WDM, Smith EB, Smith RA. Physicochemical approaches to the mode of action of general anesthetics. *Anesthesiology* 1972; **36**: 339–351.
2. Bishop BE, Laverty R. Dose-dependent reduction by Ro15-4513 in mice of the effects of ethanol and some other general depressant drugs. *European Journal of Pharmacology* 1989; **162**: 265–271.
3. Dolin SJ, Halsey MJ, Little HJ. Effects of the calcium channel activator Bay K 8644 on general anaesthetic potency in mice. *British Journal of Pharmacology* 1988; **94**: 413–422.
4. Martin DC, Abraham JE, Plagenhoef M, Aronstam RS. Volatile anesthetics and NMDA receptors. Enflurane inhibition of glutamate-stimulated [^{3}H]MK-801 binding and reversal by glycine. *Neuroscience Letters* 1991; **132**: 73–76.
5. Jones MV, Brooks PA, Harrison NL. Enhancement of γ-amino butyric acid-activated Cl$^-$ currents in cultured rat hippocampal neurones by three volatile anaesthetics. *Journal of Physiology (London)* 1992; **449**: 279–293.
6. Facklam M, Schoch P, Haefely WE. Relationship between benzodiazepine receptor occupancy and potentiation of γ-amino butyric acid-stimulated chloride flux in vitro of four ligands of differing intrinsic efficacies. *Journal of Pharmacology and Experimental Therapeutics* 1992; **261**: 1106–1112.
7. Suzdak PD, Schwartz RD, Skolnick P, Paul SM. Ethanol stimulates γ-amino butyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. *Proceedings of the National Academy of Sciences USA* 1986; **83**: 4071–4075.
8. Galindo A. Effects of procaine, pentobarbital and halothane on synaptic transmission in the central nervous system. *Journal of Pharmacology and Experimental Therapeutics* 1969; **169**: 185–195.
9. Weight FF, Lovinger DM, White G, Peoples RW. Alcohol and anesthetic actions on excitatory amino acid-activated ion channels. *Annals of the New York Academy of Sciences* 1991; **625**: 97–106.
10. Puil E, el-Beheiry H, Baimbridge KG. Anesthetic effects on glutamate-stimulated increase in intraneuronal calcium. *Journal of Pharmacology and Experimental Therapeutics* 1990; **255**: 955–961.
11. Hunt WA, Mullin MJ. Effects of ethanol exposure on brain sodium channels. *Alcohol and Drug Research* 1986; **6**: 419–422.
12. Marks SS, Watson DL, Carpenter CL, Messing RO, Greenberg DA. Comparative effects of chronic exposure to ethanol and calcium channel antagonists on calcium channel antagonist receptors in cultured neural (PC12) cells. *Journal of Neurochemistry* 1989; **53**: 168–172.
13. Terrar DA. Structure and function of calcium channels and the actions of anaesthetics. *British Journal of Anaesthesia* 1993; **71**: 39–46.
14. Suzdak PD, Glowa JR, Crawley JN, Schwartz RD, Skolnick P, Paul SM. A selective imidazobenzodiazepine antagonist of ethanol in the rat. *Science* 1986; **234**: 1243–1247.
15. Hoffman PL, Tabakoff B, Szabo G, Suzdak PD, Paul SM. Effect of an imidazobenzodiazepine, Ro15-4513, on the incoordination and hypothermia produced by ethanol and pentobarbital. *Life Sciences* 1987; **41**: 611–619.
16. Ticku MK, Kulkarni K. Molecular interactions of ethanol with GABAergic system and potential of Ro15-4513 as an ethanol antagonist. *Pharmacology, Biochemistry and Behavior* 1988; **30**: 501–510.
17. Koblin DD, Deady JE, Dong DE, Eger EI. Mice tolerant to nitrous oxide are also tolerant to alcohol. *Journal of Pharmacology and Experimental Therapeutics* 1980; **213**: 309–312.
18. Sebel PS, Flynn PJ, Ingram DA, Effects of nitrous oxide on visual, auditory and somatosensory evoked potentials. *British Journal of Anaesthesia* 1984; **56**: 1403–1407.
19. Huang C, Liu G, Hsiao C-F, Huang RH. Nitrous oxide inhibits auditory and visual responses of granule cells in the cerebellum. *Brain Research* 1991; **553**: 129–134.
20. Dzoljic M, Rupreht J, Erdmann W, Stijnen TH, Briemen LJ, Dzoljic MR. Behavioral and electrophysiological aspects of nitrous oxide dependence. *Brain Research Bulletin* 1994; **33**: 25–31.
21. Bigler ED. Neurophysiology, neuropharmacology and behavioral relationships of visual system evoked after-discharges. *Biobehavioral Reviews* 1977; **1**: 95–112.
22. Berkowitz BA, Finck AD, Hynes MD, Ngai SH. Tolerance to nitrous oxide analgesia in rats and mice. *Anesthesiology* 1979; **51**: 309–312.
23. Schubert A, Licina MG, Lineberry PJ. The effect of ketamine on human somatosensory evoked potentials and its modification by nitrous oxide. *Anesthesiology* 1990; **72**: 33–39.
24. Franks NP, Lieb WR. Selective actions of volatile general anaesthetics at molecular and cellular levels. *British Journal of Anaesthesia* 1993; **71**: 65–76.
25. Schwartz AE, Maneksha FR, Kanchuger MS, Sidhu US, Poppers PJ. Flumazenil decreases the minimum alveolar concentration of isoflurane in dogs. *Anesthesiology* 1989; **70**: 764–766.
26. Moody EJ, Skolnick P. The imidazobenzodiazepine Ro15-4513 antagonizes methoxyflurane anesthesia. *Life Sciences* 1988; **43**: 1269–1276.
27. Mandema JW, Gubbens-Stibbe JM, Danhof M. Stability and pharmacokinetics of flumazenil in the rat. *Psychopharmacology* 1991; **103**: 384–387.

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Pancuronium increases pulmonary arterial pressure in lung injury

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Summary

We studied 25 mongrel dogs who were anaesthetized and their lungs ventilated for investigation of the effects of pancuronium on pulmonary arterial pressure (PAP) in the normal lung, in oleic acid-induced lung injury and in lung injury with hypoxaemia. In the normal lung, PAP was not affected by pancuronium. During lung injury, however, PAP was increased from 21.5 (SD 2.8) to 24.6 (4.2) mm Hg ($P<0.01$) and from 22.0 (4.2) to 27.0 (5.8) mm Hg ($P<0.01$) after pancuronium 0.08 mg kg^{-1} and 0.16 mg kg^{-1}, respectively, and from 26.0 (2.9) to 37.1 (3.1) mm Hg after pancuronium 0.16 mg kg^{-1} when hypoxaemia was present ($P<0.01$). The increase in PAP induced by pancuronium was associated with increases in cardiac output and pulmonary vascular resistance. Pretreatment with phentolamine attenuated the pancuronium-induced increase in PAP. The increase in PAP induced by pancuronium was also reduced by vagotomy. If these results in dogs are relevant clinically, then pancuronium should be avoided as a neuromuscular blocker in lung injury. (*Br. J. Anaesth.* 1996;**77**:526–529)

Key words

Neuromuscular block, pancuronium. Lung, damage. Lung, intravascular pressures. Dog.

Pancuronium increases heart rate and systemic arterial pressure in both humans and animals. It has been shown that these increases result from the vagolytic effect of pancuronium on the heart[1 2] and its indirect sympathomimetic effect[3–5]. Pancuronium also changes airway resistance. When administered at low doses (less than 0.14 mg kg^{-1}), pancuronium enhances the increase in airway resistance induced by vagal stimulation, which is thought to be the effect of block of muscarinic receptor subtype 2 (M_2) by pancuronium. When administered at larger doses, pancuronium attenuates the increase in airway resistance, which is thought to be the effect of block of muscarinic receptor subtypes 1 and 3 (M_1 and M_3)[6 7]. The effects of pancuronium on the pulmonary circulation, however, have not received much attention. In the pulmonary circulation, M_1, M_2 and M_3 receptors have been identified in both humans and animals[8]. Recently, Altiere and colleagues[9] and McCormack and colleagues[10] have shown, using isolated pulmonary arterial strips, that the pulmonary circulation is functionally innervated by M_3 receptors, and M_3 antagonists contracted acetylcholine-dilated pulmonary arteries.

Therefore, we have investigated the changes in pulmonary arterial pressure in response to pancuronium in normal lung and in oleic acid-induced lung injury in dogs. The possible neural mechanism in the responses were also investigated.

Materials and methods

The study was approved by the Animal Care Committee of the University of Tokyo.

Adult mongrel dogs of both sexes (10–13 kg) were sedated with ketamine 100 mg i.m. Anaesthesia was induced with α-chloralose 100 mg kg^{-1} and urethane 100 mg kg^{-1} i.v. The lungs were ventilated via a tracheostomy using a Harvard respirator (Model 618). Tidal volume was adjusted to maintain an arterial $P\text{CO}_2$ of 4.8–5.6 kPa at a rate of 16 bpm at baseline. Ventilator settings were not changed during the experiment, except the inspired fraction of oxygen ($F\text{I}_{\text{O}_2}$), as described below. Anaesthesia was maintained with α-chloralose 25 mg kg^{-1} and urethane 25 mg kg^{-1} i.v. when necessary. Lactated Ringer's solution was infused at a rate of 3 ml kg^{-1}. Dextran 40 was infused within the first hour after injection of oleic acid to maintain systolic systemic arterial pressure greater than 90 mm Hg.

The femoral artery was cannulated for measurement of mean arterial pressure (MAP) and sampling of arterial blood. Arterial blood-gas tensions were measured using an automatic blood-gas analyser (Stat Profile 3, Nova, MA, USA). A Fr.5 balloon-tipped pulmonary artery catheter was advanced into the pulmonary artery via the femoral vein for measurement of pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), cardiac output (CO) using the thermodilution method (MTC-6210, Nihon Kohden), and for injection of oleic acid into the central vein. The correct positioning of the pulmonary artery catheter was confirmed by PAP wave and verified further by postmortem examination. Heart rate was monitored (ECG lead II) and pulmonary vascular resistance (PVR) was calculated using the formula: PVR=(PAP−PAWP)/CO (mm Hg $litre^{-1}$ min^{-1}).

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After the experimental preparation, the dogs were placed in the prone position. Oleic acid 0.12 ml kg^{-1} (Sigma) was infused into the central vein within 1 min. Arterial blood-gas tensions were measured every 30 min thereafter. Pa_{O_2}/FI_{O_2} was used as the parameter of the severity of lung injury. The effects of pancuronium during lung injury were tested only when Pa_{O_2}/FI_{O_2} was within 100–140. If Pa_{O_2}/FI_{O_2} remained greater than 140 at 3 h after the first dose of oleic acid, further oleic acid (0.06 ml kg^{-1}) was given.

Twenty-five dogs were allocated to one of four groups.

Group I: effects of pancuronium on PAP in the normal lung, during lung injury and during lung injury with hypoxaemia (*n*=10). After the experimental preparation, baseline measurements, including PAP, MAP, HR and arterial blood-gas tensions, were undertaken with an FI_{O_2} of 0.21. The effects of i.v. pancuronium (Sankyo, Tokyo, Japan) 0.08 mg kg^{-1} and 0.16 mg kg^{-1} were investigated in an alternate sequence. The injections of two doses were separated by more than 90 min. FI_{O_2} was then increased to maintain Pa_{O_2} greater than 12 kPa while lung injury was induced by oleic acid. During lung injury, when Pa_{O_2}/FI_{O_2} was 100–140, the effects of pancuronium i.v. at the two doses were investigated as was done in the normal lung. FI_{O_2} was then decreased to produce a Pa_{O_2} of 6–8 kPa (hypoxaemia). The effects of pancuronium 0.16 mg kg^{-1} were studied during lung injury with hypoxaemia.

Group II: effects of pancuronium on cardiac output and pulmonary vascular resistance in lung injury (*n*=5). Lung injury was induced as in group I while FI_{O_2} was increased to maintain Pa_{O_2} greater than 12 kPa. The effects of pancuronium 0.16 mg kg^{-1} were investigated during lung injury. The maximum increase in PAP within 60 s after administration of pancuronium was recorded. CO was then measured using thermodilution, followed immediately by measurement of PAWP. The value of PAWP was read from a pre-calibrated recorder chart (paper speed=10 mm s^{-1}), 15 s after inflation of the pulmonary artery catheter balloon at the end of expiration. Consequently, measurements of PAP, CO and PAWP were finished within 2.5 min after administration of pancuronium in all animals. Calculation of PVR using PAP, PAWP and CO at different times may introduce some error. This was minimal as in preliminary experiments we found the influence of pancuronium 0.16 mg kg^{-1} on PAP, CO, and PAWP remained stable for more than 3 min, and a cardiac output monitor with good reproducibility (*n*=10, coefficient of variance=4%) was used.

Group III: influence of pretreatment with an α adrenergic blocker on the pancuroniuminduced increase in PAP (*n*=5). Lung injury was induced as in group II. The effects of pancuronium 0.16 mg kg^{-1} were then investigated. Eighty minutes later, phentolamine 2 mg kg^{-1} (Ciba-Geigy, Swiss) was administered into the central vein over 60 s. The effects of pancuronium 0.16 mg kg^{-1} were investigated again 10 min after injection of phentolamine.

Group IV: influence of vagotomy on the pancuronium-induced increase in PAP (*n*=5). One hour after the effects of pancuronium 0.16 mg kg^{-1} during lung injury were investigated as in group II, bilateral vagotomy was performed at the level of the first tracheal ring. The effects of pancuronium 0.16 mg kg^{-1} were investigated 30 min after vagotomy.

DATA ANALYSIS

All values are expressed as mean (SD), and statistical difference was accepted at $P<0.05$. Variables before administration of pancuronium were compared with those after pancuronium by paired Student's *t* test. In groups III and group IV, the increase in PAP induced by pancuronium during normal innervation was compared with that under the conditions of α block or vagotomy using the paired Student's *t* test.

Results

EFFECTS OF PANCURONIUM ON PAP IN NORMAL LUNG AND LUNG INJURY

In the normal lung, pancuronium had no significant effect on PAP, MAP or HR. During lung injury, however, pancuronium 0.08 mg kg^{-1} and 0.16 mg kg^{-1} increased PAP by 3.1 mm Hg and 5.0 mm Hg, respectively ($P<0.01$). HR was also increased significantly by both doses of pancuronium ($P<0.01$). The increase in PAP induced by pancuronium lasted for 3–10 min. During lung injury with hypoxaemia (Pa_{O_2} 6.8 (0.5) kPa), pancuronium 0.16 mg kg^{-1} increased PAP by 11.1 mm Hg ($P<0.01$), which lasted 5–15 min (fig.1, table 1).

EFFECTS OF PANCURONIUM ON CARDIAC OUTPUT AND PULMONARY VASCULAR RESISTANCE IN LUNG INJURY

The pancuronium-induced increase in PAP during lung injury was associated with simultaneous increases in CO ($P<0.05$) and PVR ($P<0.01$) indicat-

Table 1 Effects of pancuronium on haemodynamic state in the normal lung, during pulmonary oedema and during pulmonary oedema with hypoxaemia (mean (SD)). (*n*=10). Pan = pancuronium; PAP = pulmonary arterial pressure (mm Hg); MAP = mean systemic arterial pressure (mm Hg); HR = heart rate (beat min^{-1}). ** $P < 0.001$ *vs* before administration of Pan

	Normal lung				Pulmonary oedema				Pulmonary oedema with hypoxaemia	
	Pan 0.08 mg kg^{-1}		Pan 0.16 mg kg^{-1}		Pan 0.08 mg kg^{-1}		Pan 0.16 mg kg^{-1}		Pan 0.16 mg kg^{-1}	
	Before	After	Before	After	Before	After	Before	After	Before	After
PAP	16.0 (2.6)	17.1 (2.9)	15.3 (3.2)	17.2 (4.8)	21.5 (2.8)	24.6 (4.2)**	22.0 (4.2)	27.0 (5.8)**	26.0 (2.9)	37.1 (3.1)**
MAP	143 (18)	141 (21)	135 (14)	137 (20)	124 (19)	129 (20)	127 (10)	136 (16)	134 (14)	144 (23)
HR	187 (23)	194 (32)	184 (29)	187 (26)	144 (25)	156 (26)**	148 (24)	169 (25)**	181 (22)	220 (18)**

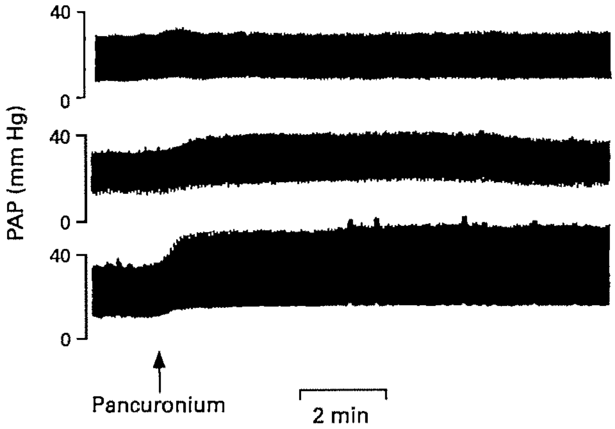

Figure 1 Effects of pancuronium 0.16 mg kg^{-1} on pulmonary arterial pressure (PAP) in normal lung (top), during lung injury induced by oleic acid (middle) and during lung injury with hypoxaemia (bottom).

ing that the increase in PAP resulted from both an increase in pulmonary blood flow and contraction of the pulmonary circulation. PAWP did not change significantly after pancuronium (table 2).

INFLUENCE OF PRETREATMENT WITH PHENTOLAMINE OR VAGOTOMY ON THE PANCURONIUMINDUCED INCREASE IN PAP

Pretreatment with the α blocker, phentolamine, decreased the pancuronium-induced increase in PAP ($P<0.05$). PAP immediately before administration of pancuronium was not significantly different from that immediately before phentolamine administration ($P>0.05$). In contrast, the increase in PAP by pancuronium after vagotomy was less than that before vagotomy ($P<0.05$). Vagotomy itself consistently increased PAP, from 21.1 (8.7) to 24.2 (11.0) mm Hg ($P<0.05$) (fig. 2).

Discussion

The results of this study showed that during lung injury, pancuronium increased pulmonary arterial pressure, especially when there was hypoxaemia. In group II, PAWP did not change when PAP was increased by pancuronium. Pulmonary capillary pressure, therefore, should increase according to the equation of Gaar and colleagues[11]. As a small increase in pulmonary intravascular pressure accelerates fluid outflux into lung interstitium and worsens lung injury in permeability lung injury[12], if our results are clinically relevant we suggest that pancuronium should be avoided as a neuromuscular blocker in lung injury.

Table 2 Effects of pancuronium during pulmonary oedema (mean (SD)) (n=5). Pan = pancuronium; PAP = pulmonary arterial pressure (mm Hg); PAWP = pulmonary arterial wedge pressure (mm Hg); CO = cardiac output (litre min^{-1}); PVR = pulmonary vascular resistance (mm Hg litre^{-1} min^{-1}). * $P < 0.05$, ** $P < 0.01$ *vs* before administration of Pan

	Before Pan	After Pan
PAP	22.0 (5.3)	27.7 (6.6)**
PAWP	5.6 (2.0)	4.9 (1.4)
CO	1.76 (0.39)	1.88 (0.47)*
PVR	9.6 (3.5)	12.6 (3.6)**

In our study, the increase in PAP in response to pancuronium was attenuated by pretreatment with an α adrenergic blocker. This suggests that high activity in α adrenergic nerves plays a role in the pancuronium-induced increase in PAP. Pancuronium has been shown to be an indirect sympathomimetic agent. It stimulates the release of catecholamines from nerve endings and inhibits neuronal uptake of noradrenaline[3, 4]. Administration of pancuronium may also increase plasma catecholamine concentrations[5]. In contrast, inhibition of the pancuronium-induced increase in PAP by pretreatment with an α blocker in our study was not complete. The increase in PAP induced by pancuronium decreased from 6.6 (2.7) mm Hg to 2.5 (0.9) mm Hg after administration of phentolamine. Therefore, there may be some other pathway by which pancuronium increases PAP.

Pancuronium is known to possess vagolytic effects by inhibiting muscarinic receptors[1, 2]. If the pancuronium-induced increase in PAP were not related to the vagus nerve, the increase in PAP by pancuronium before vagotomy would be same as that after vagotomy. In contrast, if the vagal pathway were the only route by which pancuronium increased PAP, there would be no change in PAP induced by pancuronium after vagotomy. In our study, the increase in PAP produced by pancuronium was 3.4 (1.9) mm Hg after vagotomy compared with 5.9 (3.5) mm Hg before vagotomy ($P<0.05$). It may be considered that the vagus plays some role in the pancuronium-induced increase in PAP.

Block of muscarinic receptors by pancuronium may involve both the heart and pulmonary circulation. The increase in cardiac output has been suggested to be the result of inhibition of atrial muscarinic receptors[1, 2]. The increase in PVR in this study, on the other hand, indicates that block of muscarinic receptors in the pulmonary circulation may also be involved in the pancuronium-induced increase in PAP. In the lungs, muscarinic receptors consist of at least three subtypes, M_1, M_2 and M_3 receptors[8]. Using isolated pulmonary arterial strips,

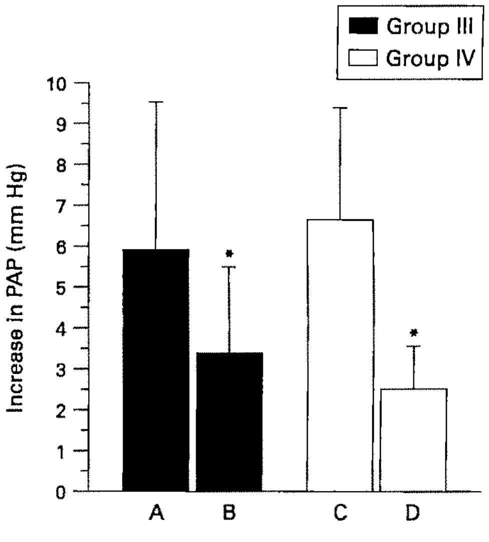

Figure 2 Increase in pulmonary arterial pressure (PAP) caused by pancuronium 0.16 mg kg^{-1} before administration of α blocker (A), after administration of α blocker (B), before vagotomy (C) and after vagotomy (D) during lung injury. *$P<0.05$ compared with before administration of α blocker or before vagotomy.

it has been found recently that the pulmonary circulation is functionally innervated by M_3 receptors and M_3 antagonists contracted acetylcholine-dilated pulmonary arteries[9 10]. We have also shown that vagotomy increased PAP in lung injury in another study[13] and in group IV in this study. As vagal activity is increased in lung injury[14] and vagotomy increased PAP during lung injury but did not alter PAP in the normal lung[13], we infer that muscarinic inhibition by pancuronium also increased PAP in lung injury *in vivo*. It is not known what muscarinic receptor subtype is responsible for the pancuronium-induced increase in PAP. However, as block of M_3 receptor causes constriction of the pulmonary artery[9 10] and large doses of pancuronium may block M_3 receptors in the airway[6], M_3 receptor involvement is likely at the doses used in this study.

References

1. Lee Son S, Waud BE, Waud DR, Phil D. A comparison of the neuromuscular blocking and vagolytic effects of ORG NC45 and pancuronium. *Anesthesiology* 1981; **55**: 12–18.
2. Lee Son S, Waud DR. Effects of non-depolarizing neuromuscular blocking agents on the cardiac vagus nerve in the guinea pig. *British Journal of Anaesthesia* 1980; **52**: 981–987.
3. Domenech JS, Garcia RC, Sasiain JMR, Loyola AQ, Oroz JS. Pancuronium bromide: an indirect sympathomimetic agent. *British Journal of Anaesthesia* 1976; **48**: 1143–1148.
4. Sait PJ, Barnes PK, Conway CM. Inhibition of neuronal uptake of noradrenaline in the isolated perfused rat heart by pancuronium and its homologues, ORG 6368, ORG 7268 and NC45. *British Journal of Anaesthesia* 1980; **52**: 313–317.
5. Nana A, Cardan E, Domokos M. Blood catecholamine changes after pancuronium. *Acta Anaesthesiologica Scandinavica* 1973; **17**: 83–87.
6. MacLagan J. Presynaptic control of airway smooth muscle. *American Review of Respiratory Disease* 1987; **136**: S54–S57.
7. Vettermann J, Beck KC, Lindahl SGE, Brichant JF, Rehder K. Actions of enflurane, isoflurane, vecuronium, atracurium, and pancuronium on pulmonary resistance in dogs. *Anesthesiology* 1988; **69**: 688–695.
8. Mak JC, Barnes PJ. Autoradiographic visualization of muscarinic receptor subtypes in human and guinea pig lung. *American Review of Respiratory Disease* 1990; **141**: 1559–1568.
9. Altiere RJ, Travis DC, Roberts J, Thompson DC. Pharmacological characterization of muscarinic receptors mediating acetylcholine-induced contraction and relaxation in rabbit intrapulmonary arteries. *Journal of Pharmacology and Experimental Therapeutics* 1994; **270**: 269–276.
10. McCormack DG, Mak JC, Minette P, Barnes PJ. Muscarinic receptor subtypes mediating vasodilation in the pulmonary artery. *European Journal of Pharmacology* 1988; **158**: 293–297.
11. Gaar KA, Taylor AE, Owens LJ, Guyton AC. Pulmonary capillary pressure and filtration coefficient in the isolated perfused lung. *American Journal of Physiology* 1967; **213**: 910–914.
12. Huchon GJ, Hopewell PC, Murray JF. Interactions between permeability and hydrostatic pressure in perfused dogs' lungs. *Journal of Applied Physiology* 1981; **50**: 905–911.
13. Yamada Y, Du HL, Suwa K, Hanaoka K. Roles of vagal innervation in the development of oleic acid-induced lung injury. *Anesthesiology* 1993; **79**: A234.
14. Roberts AM, Bhattacharya J, Schultz HD, Coleridge HM, Coleridge JCG. Stimulation of pulmonary vagal afferent C-fibers by lung edema in dogs. *Circulation Research* 1986; **58**: 512–522.

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Efficacy of intraoperative heat administration by ventilation with warm humidified gases and an oesophageal warming system

E. BECK, M. LANGER, P. DI MAURO AND P. PRATO

Summary

We measured changes in body temperature in 12 hypothermic (mean aural temperature 34.4 (SD 1.0) °C) pigs during general anaesthesia with an open abdominal cavity and the effect of two warming systems: heating of inspired gases to 39 °C (intratracheal temperature) and oesophageal warming to 39 °C by a water perfused oesophageal heat exchanger. Each animal underwent both treatments and the control period in random sequence. Each condition was studied over 1 h. No additional protection against heat loss (drapes, blankets, i.v. fluids warming, etc.) was used. Anaesthesia, room temperature and relative humidity, amount and temperature of infusions and extension of exposed visceral surfaces were standardized. Mean decrease in body temperature was 1.0 (0.7) °C ($P<0.005$) without warming and 0.6 (0.2)°C ($P<0.005$) with heated inspired gases: this difference was not statistically significant. Oesophageal warming was very efficient as mean body temperature did not change significantly (–0.1 (0.2) °C; ns). (*Br. J. Anaesth.* 1996;**77**:530–533)

Key words

Anaesthetic techniques, hypothermia. Equipment, warming devices. Temperature, body. Temperature, monitoring. Temperature, effects. Pig.

Mild hypothermia is relatively frequent during and after surgery under general anaesthesia. Several factors contribute to body heat loss: inhibition of the hypothalamus, peripheral vasodilatation induced by anaesthetic agents, paralysis, exposure of the viscera to the atmosphere and large amounts of i.v. infusions at room temperature. Mild hypothermia is not generally a problem during operation. However, in the immediate postoperative period, activation of some physiological mechanisms of thermogenesis (metabolic heat production, muscles activity, shivering) with a consequent increase in oxygen consumption and peripheral vasoconstriction are untoward and may even be harmful in patients with impaired cardiovascular reserve[1 2]. Moreover, hypothermia has been implicated in some cases of delayed recovery from general anaesthesia[3].

Several methods are commonly used to reduce body heat loss. Heating inspired gases[4–8] and oesophageal warming[9–11] are easily applied during surgery and have been proposed for providing (central) warming, which is probably more "physiological" than other methods which deliver heat peripherally (warming the operating room, warm mattresses, thermal blankets, infrared heating lamps, forced air warmers[1–2 12–18]).

The aims of this study were: to evaluate, in an animal model, under strictly controlled conditions, changes in body temperature during general anaesthesia with an open abdominal cavity, with standardization of most confounding factors such as anaesthesia, room temperature, amount and temperature of infusions, and extension of exposed visceral surfaces; to evaluate, in the same controlled conditions, the efficacy of two warming systems (heating inspired gases and oesophageal warming) in reducing body heat loss.

Materials and methods

After obtaining approval from the Ethics Committee of our institution, we studied 12 female, 3-month-old White Landrace pigs, weighing 18.4 (SD 1.2) kg. These animals were chosen as, among non-primate laboratory animals, the pig is the most comparable with adult humans[19].

Each animal underwent three study periods (control; heating of inspired gases; oesophageal warming) in a randomized sequence according to a Latin square design. The sample size was based on the results of an unpublished pilot study, by assuming a type I error (α) of 0.05 and a type II error (β) of 0.2, taking into account the randomization design and the statistical analysis method (repeated-measures analysis of variance)[20].

Anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with 1.5% enflurane and fentanyl 2–3 μg kg^{-1} h^{-1}. Neuromuscular block was produced with pancuronium 50–60 μg kg^{-1} h^{-1}. Mechanical ventilation (Servo ventilator 900A, Elema, Schönander, Sweden) via a tracheostomy was set at 3.8–4.2 litre min^{-1} to maintain a Pa_{CO_2} of 4.7–6.0 kPa. The total inspiratory time was 35% (25% inspiration+10% inspiratory pause).

A carotid artery catheter and a 5-French gauge pulmonary artery catheter were inserted for haemodynamic monitoring and blood sampling. Arterial pressure (AP), pulmonary artery pressure (PAP), central venous pressure (CVP) and pulmonary

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wedge pressure (PWP) were measured with HP 1290A pressure transducers and a 78354A monitor (Hewlett Packard GmbH, Böblingen, Germany). Cardiac output (CO) was measured by thermodilution (mean of three measurements at expiratory pause) with a 9520A CO computer (Edwards, Santa Ana, CA, USA). Blood pH, $P\text{co}_2$ and $P\text{o}_2$ were determined with an IL1302 analyser, and haemoglobin and oxygen saturation with an IL802 co-oximeter (Instrumentation Laboratory, Milano, Italy).

Room, oesophageal, tracheal and aural temperatures, and four cutaneous temperatures (anterior leg (A), nipple (B), thigh (C) and calf (D)) were monitored with an MC9200 electronic thermometer (Exacon, Roskilde, Denmark) using site-specific probes (Exacon, Roskilde, Denmark). Relative humidity of the room was measured with a standard hygrometer.

I.v. infusions (at room temperature) were standardized at 10 ml kg^{-1} h^{-1}. A laparotomy was performed with standardized partial exposure of the viscera. The surgical drapes were then removed and the animal was left exposed to the environment.

Each animal underwent three conditions in randomized sequence.

(1) Inspired gases were warmed and saturated using a Kontron Pearl Humidifier 4150 (Kontron Instruments, Milan, Italy) modified to exceed the 37 °C temperature limit. The humidifier was adjusted to obtain an inspiratory tracheal temperature of 39±0.5 °C. The tracheal temperature probe also allowed measurement of end-expiratory gas temperature. The inspiratory branch of the ventilator circuit was wrapped in aluminium sheets. The oesophageal heat exchanger was not in place. The 60-min study started as soon as the inspiratory tracheal temperature was stabilized at 39±0.5 °C for at least 5 min.

(2) The oesophageal warmer is composed by a water perfused oesophageal heat exchanger and a water heating pump (water flow 4 litre min^{-1}) with a built-in thermostat adjustable up to 42 °C (Thermal Therapy System (TTS) TT8200, Exacon, Roskilde, Denmark). The oesophageal heat exchanger consists of a light rigid inner supply tube, surrounded by a 50-cm long, non-elastic and thin-walled outer tube (surface area ~0.05 m^2). Distilled water is circulated through the inner tube to the tip, fills up the entire volume of the outer tube and returns to the pump through the proximal end of the oesophageal tube. After the oesophageal heat exchanger was placed, the system thermostat was set to obtain an oesophageal temperature of 39±0.5 °C. A Kontron Pearl Humidifier 4150 (Kontron Instruments, Milan, Italy) at room temperature was used in the ventilator circuit. The 60-min study started as soon as oesophageal temperature was stabilized at 39±0.5 °C for at least 5 min.

(3) No warming systems were used. The oesophageal heat exchanger was not in place and the Kontron humidifier was at room temperature.

Temperature, haemodynamic measurements and blood samples were obtained at the beginning (pre) and end (post) of each 60-min study period. The following variables were calculated:

Mean skin temperature (MST) according to Ramanathan's formula[21]:

$$\text{MST }(^\circ\text{C})=0.3\times(T\text{A}+T\text{B})+0.2\times(T\text{C}+T\text{D})$$

Mean body temperature (MBT) according to Colin and colleagues' formula[22]:

$$\text{MBT }(^\circ\text{C})=0.66\times T\text{aural}+0.34\times\text{MST}$$

Total body heat (TBH) relative to 0 °C according to Burton's formula[23]:

$$\text{TBH (kJ)}=\text{MBT}\times3.47\times\text{body weight (kg)}$$

Oxygen consumption ($\dot{V}\text{o}_2$) according to Fick's equation:

$$\dot{V}\text{o}_2\ (\text{ml min}^{-1})=10\times Ca_{O_2}-Cv_{O_2}\ (\text{ml 100 ml}^{-1})\times\text{CO (litre min}^{-1})$$

Right to left shunt fraction ($\dot{Q}\text{va}/\dot{Q}\text{t}$) according to the following equation:

$$\dot{Q}\text{va}\dot{Q}/\text{t}=(Cc'_{O_2}-Ca_{O_2})/(Cc'_{O_2}-Cv_{O_2})$$

where Cc'_{O_2}(ml 100 ml^{-1})=1.34×Hb (g 100 ml^{1})+0.003×($P\text{I}_{O_2}$ (mm Hg)− $P\text{a}_{CO_2}$ (mm Hg); Ca_{O_2} (ml 100 ml^{-1})=1.34×Hb×$S\text{a}_{O_2}$ (fraction)+0.003×$P\text{a}_{O_2}$ (mm Hg); and Cv_{O_2} (ml 100 ml^{1})=1.34×Hb× $S\bar{v}_{O_2}$ (fraction)+0.003×$P\bar{v}_{O_2}$ (mm Hg).

At the end of the experiment, specimens of tracheal and oesophageal wall were obtained to detect possible heat-related damage[24].

Statistical analysis was performed using the SAS/GLM procedure, release 6.03 (SAS Institute Inc., Cary, NC, USA) on a AST Bravo LC 3/33s personal computer (AST Research, Inc., Irvine, CA, USA).

Results

Each animal completed both treatments and the control period.

Data for all measured variables at the beginning (pre) of each 60-min condition, and differences between the beginning and final values (post–pre) are shown in table 1. Pre values were not significantly different between the three conditions.

Room temperature and relative humidity were monitored continuously and did not change significantly during the experiment. All measured temperatures and derived variables (MST, MBT and TBH) decreased significantly under both control ($P<0.005$) and warm inspired gas ($P<0.005$) conditions. With oesophageal warming, only cutaneous temperature A (anterior leg) showed significant variations.

As shown by the variation in all measured body temperatures and derived variables, heat loss was significantly greater during the control period than during oesophageal warming, while the difference between the control period and that during warming of inspired gases was not statistically significant, except for nipple temperature (B) and MST (table 1).

$\dot{V}\text{o}_2$ decreased significantly ($P<0.001$) by 8–15% during the control period and during the two treatments (table 1), but there were no significant differences between the three conditions. $\dot{Q}\text{va}/\dot{Q}\text{t}$ did not change significantly and there were no differences between the three conditions.

The animals were haemodynamically stable throughout the experiment.

There were no pathological changes at the histological examination of both tracheal and oesophageal walls at the end of the study.

Table 1 Temperatures and haemodynamic variables measured at the beginning (pre) (mean (SD)) and differences between the beginning and final values (post-pre) (mean (SEM)) during control conditions, warming of inspired gases (Hum) and oesophageal warming (TTS). HR = heart rate; CO = cardiac output; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PWP = pulmonary wedge pressure; CVP = central venous pressure; TSR = total systemic resistances; TPR = total pulmonary resistances; $\dot{V}o_2$ = oxygen consumption; $\dot{Q}va/\dot{Q}t$ = shunt fraction. ** $P < 0.01$ *vs* Pre values; † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$ *vs* control

	Pre			Post-Pre		
	Control	Hum	TTS	Control	Hum	TTS
Aural temp. (°C)	34.6 (0.7)	34.4 (0.9)	34.1 (1.2)	−0.8 (0.1)**	−0.5 (0.1)**	−0.1 (0.1)†
Skin temp. A (°C)	33.0 (0.9)	32.9 (0.8)	32.7 (1.1)	−0.8 (0.1)**	−0.5 (0.1)**	−0.3 (0.1)**††
Skin temp. B (°C)	33.2 (0.7)	33.0 (0.9)	32.7 (1.4)	−1.0 (0.1)**	−0.6 (0.1)**†	−0.2 (0.1)†††
Skin temp. C (°C)	34.0 (0.9)	33.8 (0.7)	33.9 (1.0)	−0.8 (0.1)**	−0.5 (0.1)**	−0.3 (0.2)††
Skin temp. D (°C)	34.1 (0.8)	33.8 (0.9)	33.9 (0.9)	−0.8 (0.1)**	−0.5 (0.1)**	−0.1 (0.1)†††
Mean skin temp. (°C)	33.7 (0.8)	33.5 (0.8)	33.4 (1.0)	−0.8 (0.1)**	−0.5 (0.1)**†	−0.2 (0.1)†††
Mean body temp. (°C)	34.2 (0.7)	34.1 (0.8)	33.9 (1.1)	−1.0 (0.1)**	−0.6 (0.1)**	−0.1 (0.1)†††
Total body heat (kJ)	2187 (151)	2175 (136)	2163 (147)	−52 (4)**	−35 (4)**	−8 (3)††
Room temp. (°C)	24.1 (0.5)	23.9 (0.7)	23.8 (0.3)	−0.1 (0.2)	−0.3 (0.2)	−0.1 (0.1)
Relative humidity (%)	48 (3)	49 (3)	48 (2)	0.1 (0.4)	0.2 (0.3)	0.1 (0.3)
HR (beat min^{-1})	130 (25)	125 (22)	120 (21)	−13 (6)	−5 (5)	−3 (5)
CO (litre min^{-1})	2.7 (0.6)	2.4 (0.6)	2.1 (0.4)†††	−0.4 (0.1)	0.2 (0.1)	0.0 (0.1)
MAP (mm Hg)	88 (9)	82 (5)	70 (9)†††	−7 (3)	0 (4)	7 (2)
MPAP (mm Hg)	19 (4)	18 (3)	17 (5)	0 (1)	1 (1)	1 (1)
PWP (mm Hg)	5 (3)	5 (3)	7 (2)	−1 (0)	1 (1)	0 (1)
CVP (mm Hg)	4 (3)	4 (3)	5 (3)	0 (0)	1 (1)	0 (0)
TSR (dyn s min^{-5})	2640 (576)	2762 (656)	2585 (475)	215 (151)	85 (138)	333 (91)
TPR (dyn s min^{-5})	429 (149)	438 (115)	438 (172)	65 (30)	53 (28)	23 (27)
$\dot{V}o_2$ (ml min^{-1})	79 (23)	78 (22)	74 (17)	−12 (5)**	−9 (5)**	−6 (5)**
$\dot{Q}va/\dot{Q}t$	0.17 (0.11)	0.14 (0.04	0.14 (0.07)	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)

Discussion

There have been several clinical studies on the effects of different warming systems in preventing perioperative hypothermia with controversial results. Both heating of inspired gases and oesophageal warming have been demonstrated as either effective and ineffective in different studies[4-11]. The "within study" and "between studies" variability of the experimental conditions (patients, type of surgery, type of anaesthesia, fluid infusions, room temperature and relative humidity, etc.) makes it difficult to compare these studies.

In our study such confounding factors were standardized and controlled carefully. Moreover, in order to maximize the differences between treatment and control conditions, we chose to avoid any system used clinically to reduce heat loss (drapes, warming of i.v. fluids, etc): during the experiment our animals became hypothermic more quickly than usually seen in anaesthetic practice (approximately 0.5 °C h^{-1}[25]). This greater heat loss may also have resulted from the smaller body size and mass of our animals compared with an adult human.

The mean decrease in temperature (aural and the four cutaneous temperatures) was approximately 1 °C h^{-1} without warming. Mean body temperature (MBT), calculated according to the formula used in humans, reflects very well this heat loss. Some may argue that the derived variables (MST, MBT and TBH) may not be quantitatively accurate because they were computed using formulae developed for humans and which might not apply to pigs. However, as we were interested in evaluating variations rather than absolute values for each condition, we believe that our results are not invalidated by the use of human formulae.

Our study clearly showed the efficacy of oesophageal warming in attenuating the decrease in MBT and TBH. Warming of inspired gases was not as effective and the reduction in heat loss was not statistically significant. The variation in efficacy may be explained by important differences in the way the two systems work. Heat transport is much higher for oesophageal warming (~5000 kJ h^{-1} from 34 to 39 °C at a water flow of 4 litre min^{-1}) than for warming of inspired gases (~8 kJ h^{-1} from 34 to 39 °C at $\dot{V}e$=4 litre min^{-1}[26]) because of the low specific heat of air compared with water. This difference appears to be important in overcoming the larger heat exchange area during warming of inspired gases (trachea and large bronchi)[27] and probably higher heat transfer efficiency of the respiratory system (as suggested by the small difference between the temperature of the expired gas and core temperature). The technical characteristics of oesophageal warming did not allow measurement of the temperature at the outlet of the oesophageal heat exchanger and consequently calculation of net heat transfer during oesophageal warming. However, the large amount of heat transported during oesophageal warming (~5000 kJ h^{-1}) would have resulted in a greater temperature change if efficiently transferred to the body.

There were no side effects in our study. Heat damage to the tracheal and oesophageal walls was not demonstrated at histological examination or by deterioration in respiratory function ($\dot{Q}va/\dot{Q}t$).

Oesophageal warming requires a specific device but it is easily used and has no complications. It is not only the most effective non-invasive core-warming system that can be used during operation, but it may also be used successfully in other non-surgical situations of severe accidental hypothermia (exposure, cold water immersion, etc.).

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References

1. Brown BR. Inadvertent hypothermia in the surgical patient. In: Nunn JF, Utting JE, Brown BR, eds. *General Anaesthesia*. London: Butterworths, 1989; 650–654.
2. Sessler DI. Temperature monitoring. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1990; 1227–1241.
3. Johnston KR, Vaugan RS. Delayed recovery from general anaesthesia. *Anaesthesia* 1988; **43**: 1024–1025.
4. Joachimsson PO, Hedstrand U, Tabow F, Hansson B. Prevention of intraoperative hypothermia during abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 330–337.
5. Ralley FE, Ramsay JG, Wynands JE, Townsend GE, Whalley DG, Delli Colli P. Effect of heated humidified gases on temperature drop after cardiopulmonary bypass. *Anesthesia and Analgesia* 1984; **63**: 1106–1110.
6. Conahan TJ, Williams GD, Apfelbaum JL, Lecky JH. Airway heating reduces recovery time (cost) in outpatients. *Anesthesiology* 1987; **67**: 128–130.
7. Stone DR, Downs JB, Paul WL, Perkins HM. Adult body temperature and heated humidification of anesthetic gases during general anesthesia. *Anesthesia and Analgesia* 1981; **60**: 736–741.
8. Ip Yam PC, Carli F. Maintenance of body temperature in elderly patients who have joint replacement surgery. *Anaesthesia* 1990; **45**: 563–565.
9. Kristensen G, Guldager H, Gravesen H. Prevention of peroperative hypothermia in abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 314–316.
10. Kulkarni P, Matson A, Bright J, Pearson J, Carli F. Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia. *British Journal of Anaesthesia* 1993; 70: 216–218.
11. Steib A, Beller JP, von Bandel M, Beck F, Chabrol JL, Otteni JC. Oesophageal thermal tube for intraoperative hypothermia in liver transplantation. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 199–202.
12. Just B, Trévien V, Delva E, Lienhart A. Prevention of intraoperative hypothermia by preoperative skin-surface warming. *Anesthesiology* 1993; **79**: 214–218.
13. Sessler DI, Moayeri A. Skin-surface warming: heat flux and central temperature. *Anesthesiology* 1990; **73**: 218–224.
14. Lennon RL, Hosking MP, Conover MA, Perkins WJ. Evaluation of a forced-air system for warming hypothermic postoperative patients. *Anesthesia and Analgesia* 1990; **70**: 424–427.
15. Gauntlett I, Barnes J, Brown TC, Bell BJ. Temperature maintenance in infants undergoing anaesthesia and surgery. *Anaesthesia and Intensive Care* 1985; **13**: 300–304.
16. Camus Y, Delva E, Just B, Lienhart A. Leg warming minimizes core hypothermia during abdominal surgery. *Anesthesia and Analgesia* 1993; 77: 995–999.
17. Giesbrecht GG, Ducharme MB, McGuire JP. Comparison of forced-air patient warming systems for perioperative use. *Anesthesiology* 1994; **80**: 671–679.
18. Ouellette RG. Comparison of four intraoperative warming devices. *AANA Journal 1993;* ***61****: 394–396.*
19. Dodds WJ. The pig model for biomedical research. *Federal Proceedings* 1982; **41**: 247–256.
20. Kirk RE. *Experimental Design*, 2nd Edn. Belmont: Brooks-Cole,1982; 142–145.
21. Ramanathan NL. A new weighting system for mean surface temperature of the human body. *Journal of Applied Physiology* 1964; **19**: 531–533.
22. Colin J, Timbal J, Houdas Y, Boutelier C, Guieu JD. Computation of mean body temperature from rectal and skin temperature. *Journal of Applied Physiology* 1971; **31**: 484–489.
23. Burton AC. Human calorimetry: the average temperature of the tissues of the body. *Journal of Nutrition* 1935; **9**: 261–280.
24. Klein EF jr, Graves SE. Hot pot tracheitis. *Chest* 1974; **65**: 225–226.
25. Robiquet P, Krivosich-Horber R. Hypotermie et neuro-anestésie: monitorage et prévention. *Cahiers d'Anesthesiologie* 1989; **37**: 195–199.
26. Hendrickx HH, Trahey GE, Argentieri MP. Paradoxical inhibition of decreases in body temperature by use of heated and humidified gases. *Anesthesia and Analgesia* 1982; **61**: 393–394.
27. Morley-Forster P. Unintentional hypothermia in the operating room. *Canadian Anaesthetists Society Journal* 1986; **33**: 516–527.

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Extraction of nitric oxide and nitrogen dioxide from an oxygen carrier using molecular sieve 5A

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Summary

Nitric oxide (NO) is effective in the management of pulmonary hypertension and shunt-related hypoxia. Nitrogen dioxide (NO_2) is formed when the gas is delivered with oxygen. Both oxides of nitrogen have well recognized adverse effects. The scavenging properties of several forms of soda lime have been investigated. A gas flow containing NO 70 ppm and NO_2 5 ppm in oxygen was introduced into a vertically mounted Waters' canister containing: (i) 125 g of molecular sieve 5A (a calcium aluminosilicate zeolite) and (ii) 135 g of soda lime containing a potassium permanganate marker. NO and NO_2 concentrations were measured at hourly intervals at the entry and exit points using an electrochemical analyser. Extraction ratios (gradient/inlet × 100) were calculated for a 24-h period. High extraction ratios (in excess of 90%) of NO and NO_2 were observed with both compounds for up to 1 h but these declined rapidly after this time with soda lime. In contrast, the molecular sieve produced extraction ratios in excess of 98% for both gases over the 24-h period. We conclude that the molecular sieve 5A is a highly effective scavenger of NO and NO_2. (*Br. J. Anaesth.* 1996;**77**:534–536)

Key words
Equipment, scavenging devices. Gases non-anaesthetic, nitric oxide. Gases non-anaesthetic, nitrogen dioxide.

Therapeutic administration of nitric oxide (NO) is complicated by the formation of nitrogen dioxide (NO_2). Extraction of NO and NO_2 by several forms of soda lime has been investigated but these failed to demonstrate high extraction ratios for both oxides of nitrogen over prolonged periods under conditions which are relevant to the clinical situation (i.e. with an oxygen-rich carrier gas and an appropriate $NO:NO_2$ ratio)[1-4].

We have investigated the extraction properties of zeolite Ca-A (known commercially as molecular sieve 5A because of its 5 Å channel aperture) under such conditions. A comparison was made with soda lime containing a potassium permanganate indicator which was shown by Pickett and colleagues to have higher extraction ratios than other forms of soda lime[1 2].

Methods

A vertically mounted Waters' canister (id 6.5 cm, length 10 cm) was filled with: (1) molecular sieve 5A, pellet size 1.5 mm, mass 125 g (BDH Chemicals, Poole, UK) or (2) soda lime, green-to-brown, 8–12 mesh, mass 135 g (Sofnolime, Molecular Products, Thaxted, Essex, UK). As the intra-crystalline space of the zeolite is normally filled with water, before use the material was dehydrated by heating at 400 °C for 24 h. A gas flow containing NO 70 ppm and NO_2 5 ppm in oxygen was introduced at a flow rate of 10 litre min^{-1}. A calibrated Bedfont EC 90 electrochemical analyser (Bedfont Scientific Limited, Upchurch, Kent, UK) was used to assess concentrations of NO and NO_2 at the entry and exit points. Measurements were recorded hourly for 24 h with each absorber. Calibration of the electrochemical analyser was verified on completion of each set of readings. Gas pressure at the entry and exit points was recorded for each compound; the gradient remained at less than 1.5 cm H_2O throughout. Extraction ratios of NO and NO_2 for each compound were calculated for the 24-h period.

Results

High extraction ratios (in excess of 90%) of NO and NO_2 were observed with both compounds for up to 1 h. Subsequent observations revealed a rapid decline in the soda lime extraction of both NO and NO_2. This was more marked for NO. In contrast, the molecular sieve gave extraction ratios in excess of 98% for both gases over the 24-h period. Complete extraction of nitrogen dioxide was observed at 24 h (figs 1, 2).

Discussion

Zeolitic molecular sieves are aluminosilicates built from corner-sharing SiO_4 and AlO_4 tetrahedra linked by the apical oxygen atoms to form frameworks of high internal surface area with regular channels and cavities of molecular dimensions[5-7]. The channel systems, which may be one-, two- or three-dimensional, may occupy more than 50% of

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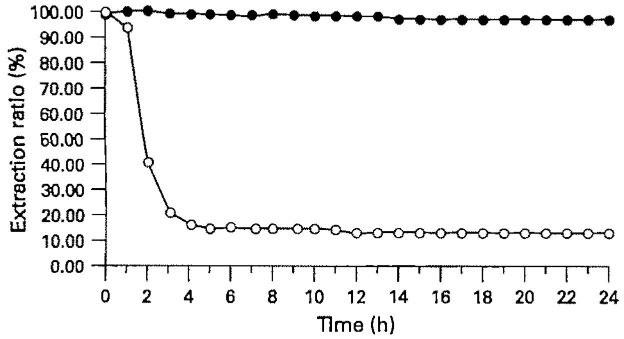

Figure 1 Extraction ratio of nitric oxide from an oxygen carrier using molecular sieve 5 (●) and soda lime (○).

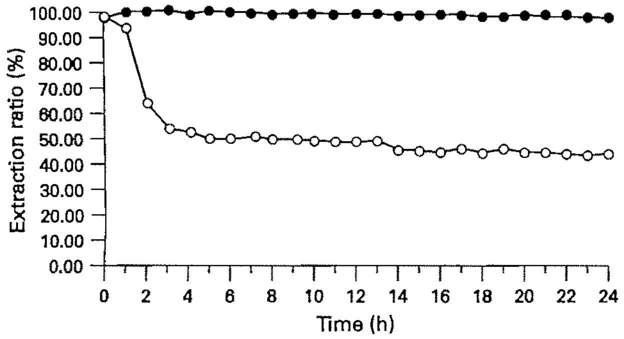

Figure 2 Extraction ratio of nitrogen dioxide from an oxygen carrier using molecular sieve 5 (●) and soda lime (○).

crystal volume. Their microporous structure enables zeolites to be used as molecular sieves as they can only adsorb molecules of certain size. The net negative charge of the framework, equal to the number of the constituent aluminium atoms, is balanced by exchangeable cations, Mn^+, located in the channels which normally also contain water. The general oxide formula of zeolite 5A is:

$$Ca_6\,[Al_{12}\,Si_{12}O_{48}]\times 27\,H_2O$$

There are approximately 40 identified zeolite minerals and at least 140 synthetic species with a wide range of compositions. The most important properties of zeolites are their ability to adsorb organic and inorganic substances and to act as cation exchangers and catalysts. Depending on pore diameter and molecular dimensions, species such as gaseous elements, ammonia, alkali metal vapours, hydrocarbons and many other organic and inorganic species may be accommodated in the intra-crystalline space of dehydrated zeolites. This process, known as molecular sieving, is a powerful method for the resolution of mixtures. Commercial applications include the drying of organics, separation of hydrocarbons and of N_2 and O_2 in air, and removal of NH_3 and CS_2 from industrial gases. Cations neutralizing the electrical charge of the aluminosilicate framework can be exchanged for other cations from solution. Zeolites often possess selectivities for certain cations, and this is used for their isolation and concentration.

Molecular sieving properties of zeolites are further modified by ion exchange. Thus sodium aluminosilicate zeolite absorbs both N_2 and O_2 while calcium aluminosilicate zeolite (molecular sieve 5A) absorbs nitrogen preferentially to oxygen. We have demonstrated slightly preferential uptake for NO_2 over NO with 5A. Uptake of both oxides of nitrogen by 5A is marginally reduced when nitrogen is used as the carrier gas (data not shown), but more efficient extraction from an oxygen-rich carrier is desirable if the compound is to be used as a scavenger. A reduction in efficiency of uptake can also be expected with the introduction of carbon dioxide and water to the carrier gas. Water vapour is a particular problem as it reacts with nitrogen dioxide to form nitric acid which leads to gradual degradation of the sieve. This problem has been encountered in the commercial production of nitric acid which involves the catalysed oxidation of ammonia. Degradation can be delayed substantially by the interposition of a bed of silica gel (US patent specification 3674429). Other properties which make the molecular sieve 5A suitable for use as a scavenger are its low cost and lack of toxicity[6].

Green-to-brown soda lime uptake of NO and NO_2 for the first hour was similar to that reported by Pickett and colleagues who showed green-to-brown Sofnolime to have a higher extraction ratio for NO than that of pink-to-white or violet-to-white Sofnolime[2]. Using a ratio of 8.6:1 of $NO{:}NO_2$, Ishibe and colleagues reported an extraction ratio of 11.9% NO for Sodasorb lime[3].

Uptake of NO appears to depend on the presence of NO_2 (indirectly proportional to the $NO{:}NO_2$ ratio). This observation is consistent with the reactions suggested by Ishibe and colleagues[4] and Kain[8]:

$$2NO + 2NO_2 + 2NaOH + Ca(OH)_2 \rightarrow 2NaNO_2 + Ca(NO_2)_2 + 2H_2O$$

$$4NO_2 + 2NaOH + Ca(OH)_2 \rightarrow 2NaNO_2 + Ca(NO_3)_2 + 2H_2O$$

The higher NO extraction ratio observed with soda lime containing a potassium permanganate marker is explained by the powerful oxidizing properties of this material. The reaction proceeds as follows[9]:

$$NO + KMnO_4 \rightarrow KNO_3 + MnO_2$$

The contribution of potassium permanganate to NO uptake is supported by our observation that the rapid reduction in NO extraction coincided with the colour change from green to brown of the soda lime. Prolonged efficiency of any form of soda lime as a scavenger of both oxides of nitrogen has yet to be demonstrated. Ishibe and colleagues reported a 5% breakout time of 30 days for NO_2 using high purity nitrogen as the carrier gas and a flow rate of 1 litre min^{-1}.

We conclude that the molecular sieve 5A was a highly effective scavenger of NO and NO_2. We have demonstrated this property with a clinically relevant gas composition over a 24-h period. Advantages over soda lime include lower cost and greater efficiency.

References

1. Pickett JA, Moors AH, Latimer RD, Mahmood N, Ghosh S, Oduro A. The role of soda lime during administration of nitric oxide. *British Journal of Anaesthesia* 1994; 72: 683–685.
2. Pickett JA, Mahmood N, Latimer RD, Powroznyk A, Ghosh S, Oduro A. Effective absorption of nitrogen dioxide with soda lime. *British Journal of Anaesthesia* 1995; 74: 107.
3. Ishibe Y, Sato S, Hayashi T, Kato N, Hata T. Effective absorption of nitrogen dioxide with soda lime. *British Journal of Anaesthesia* 1995; 74: 107.
4. Ishibe Y, Sato S, Hayashi T, Kato N, Hata T. Absorption of nitrogen dioxide and nitrogen dioxide by soda lime. *British Journal of Anaesthesia* 1995; 75: 330–333.
5. Meier WM, Olson DH. *Atlas of Zeolite Structure Types*. Oxford: Butterworths, 1992.
6. Breck DW. *Zeolite Molecular Sieves: Structure, Chemistry and Use*. London: John Wiley, 1974.

7. Barrer RM. *Zeolites and Clay Minerals as Sorbents and Molecular Sieves*. London: Academic Press, 1978.
8. Kain ML. Higher oxides of nitrogen in anaesthetic gas circuits. *British Journal of Anaesthesia* 1967; **39**: 382–387.
9. Austin AT. The chemistry of the higher oxides of nitrogen as related to the manufacture, storage and administration of nitrous oxide. *British Journal of Anaesthesia* 1967; **39**: 345–350.

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Sevoflurane degradation to compound A in anaesthesia breathing systems

D. D. CUNNINGHAM, S. HUANG, J. WEBSTER, J. MAYORAL AND R. W. GRABENKORT

Summary

Determination of an effective rate constant and activation energy allowed the application of steady-state theory to predict concentrations of compound A from sevoflurane concentrations, fresh gas flow rate, absorbent temperature and amount of absorbent. Studies by eight research groups were compared. Lower concentrations of compound A than predicted were observed at low flow rates, suggesting that its degradation by the absorbent is important in limiting the maximum observed concentrations in closed and low-flow breathing systems. Trial-to-trial and batch-to-batch variations in compound A concentrations were observed in model system tests of commercial and pilot-plant absorbents. Chemical modification of the absorbent with glycerol lowered concentrations of compound A, possibly by formation of a nucleophilic addition product. An ideal chemical scavenger would remain stable and non-volatile in the absorbent before irreversibly reacting with compound A to form a stable non-volatile product. (*Br. J. Anaesth.* 1996;**77**:537–543)

Key words

Anaesthetics volatile, sevoflurane. Carbon dioxide, absorption. Equipment, breathing systems.

Sevoflurane may degrade to form compound A and other degradation products (fig. 1). Methanol may further add to compounds C, D and E to form progressively larger molecular weight degradation products (structures not shown). In most studies reported in the literature, the concentration of compound A increases to a near steady-state concentration[1-14]. In this study, determination of an effective rate constant and activation energy allowed the application of a steady-state theory to predict steady-state compound A concentrations from sevoflurane concentrations, fresh gas flow rate, absorbent temperature and amount of absorbent. Development of the theoretical model allowed comparison of results from eight research groups during July 1995. Confirmation of the theory was attempted using a model breathing system with standard and modified absorbent canisters.

The composition of the absorbent has also been viewed as a factor in the generation of compound A[2,3,9,13-17]. Pilot-plant batches of absorbent with different concentrations of sodium hydroxide and potassium hydroxide were tested in a model breathing system under conditions designed to produce high concentrations of compound A. The possible role of moisture is discussed.

Previous detection of compound B in low-flow breathing systems[3,8,10,13,14] suggested that addition of an alcohol to compound A readily occurred. Laboratory batches of absorbent were modified with two non-volatile alcohols, glycerol and polyvinyl alcohol, and tested.

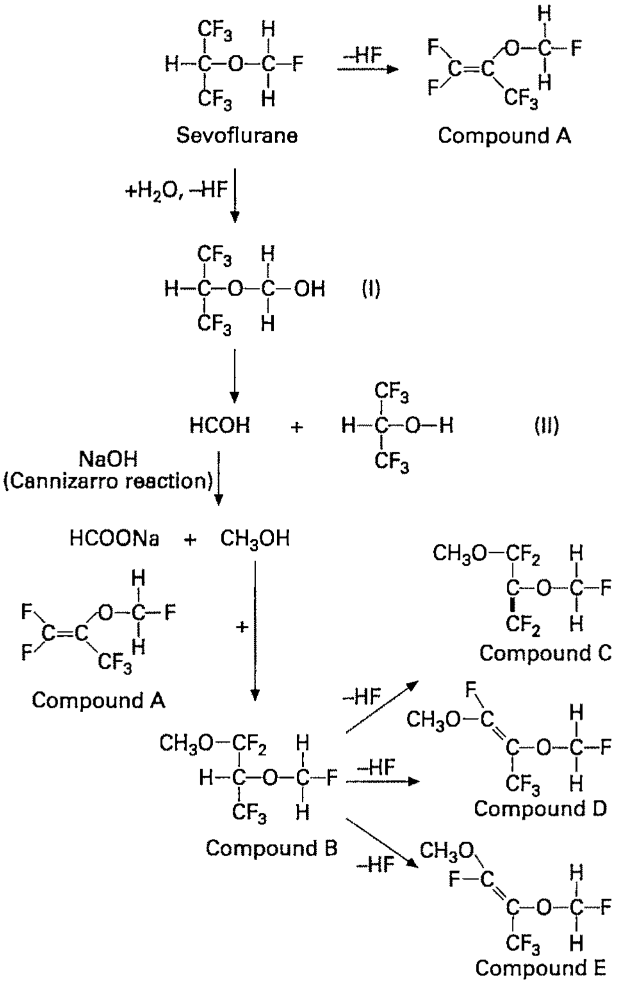

Figure 1 Reaction scheme for the degradation of sevoflurane in the presence of base.

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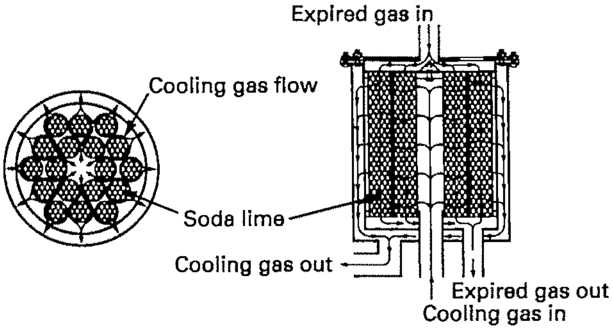

Figure 2 Schematic diagram of the modified absorbent canister. An orifice plate near the top directed the expired gas flow through the soda lime. A Dayton centrifugal fan introduced room air into the centre of the device, then around the cylinders to side holes at the periphery, and down the outside to the bottom.

Materials and methods

Simulated clinical conditions were produced using a Drager Narcomed anaesthesia machine with ventilator, Drager vaporizer, Marquest humidifier, breathing system and humidification chamber with a Gibeck heavy wall test lung attached to the y-site. Standard conditions of 1.5% sevoflurane, oxygen 250 ml min^{-1}, nitrous oxide 250 ml min^{-1} and carbon dioxide 340 ml min^{-1} into the y-site, tidal volume 500 ml, 16 bpm and carbon dioxide absorbent 1 kg were monitored using a Datex Capnomac Ultima gas analyser, unless otherwise noted. The carbon dioxide flow rate was large to produce high temperatures in the absorbent and production of compound A.

A range of temperatures for the Arrhenius plot (fig. 2) was generated using standard conditions, except for carbon dioxide 0–400 ml min^{-1}. Flow rate dependance was studied over the range 0.5–4 litre min^{-1}, otherwise using standard conditions. The rates were tested randomly and each held constant until a near steady-state compound A concentration was reached. Sevoflurane concentrations of 1.5% and 4.0% were used to test concentration dependence. One batch of Sodasorb was separated into 4, 6, 8 and 12 mesh fractions. The amounts of 4 and 12 mesh material were insufficient for testing.

Absorption of compound A to materials in the breathing system was tested using 0.7–3.4 ppm of compound A in 1–5% sevoflurane without absorbent in the canisters. Temperatures were measured with custom-made type K thermocouples using a National Instruments A/D converter with Lab View software. Forced air cooling was conducted using modified absorbent canisters constructed using 18 equally spaced 0.5-mm thick metal cylinders which were inserted in place of the standard double canister (fig. 2). Convective cooling was conducted using canisters with 19 cylinders (0.5–1.2 mm) without the outer baffled shroud shown in figure 2. Laboratory batches of absorbent were prepared with a water content of approximately 35%, passed through a grinder with 3–4 mm holes in the extrusion plate, and dried further to values reported before use.

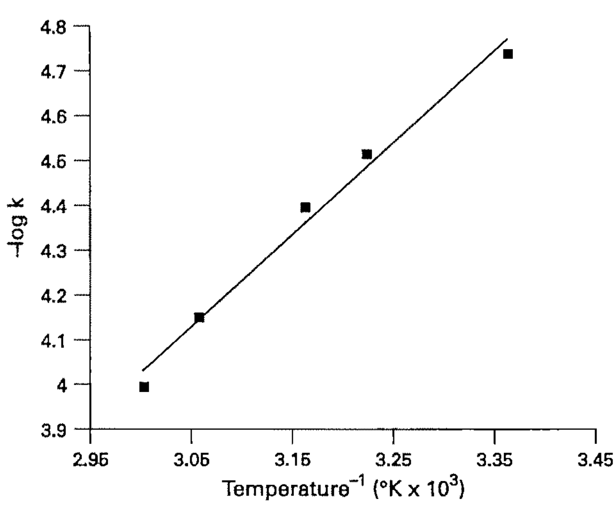

Figure 3 Arrhenius plot of near steady-state rates of formation of compound A against 1/*T*. Slope =−2027 °K, RSD=7%.

Concentrations of compound A were measured using a gas chromatography method described previously[18]. Standard addition/recovery experiments performed by two analysts in the range 4–32 ppm were found to give an overall recovery of 102% (n=12, range 88–117%, sd 9%). The variation in the standard addition/recovery results included any variation in the preparation of the samples, and the normal variation in the assay. Generally, concentrations of compound A were measured in the model breathing system every 15–30 min for at least 150 min. For convenience, only the maximum concentration found during each experiment is reported.

THEORY

A steady-state approximation was formulated to predict the steady-state concentration of compound A based on the factors of sevoflurane concentration, fresh gas flow rate, temperature and amount of absorbent. At steady-state, the amount of compound A formed in the breathing system is assumed to be equal to the amount of compound A carried out of the system by the fresh gas flow, as shown in equation (1):

$(V \times k \times [\text{sevo}]) - ([\text{cpd A}] \times \text{fresh gas flow rate}) = 0$ (1)

where V=volume of reaction, k=effective rate constant, [sevo]=volatile fraction of sevoflurane, and [cpd A]=near steady-state concentration of compound A in the breathing system. As the degradation reaction probably occurs in the highly basic aqueous coating over the insoluble portion of the absorbent, the reaction volume was taken as the approximate

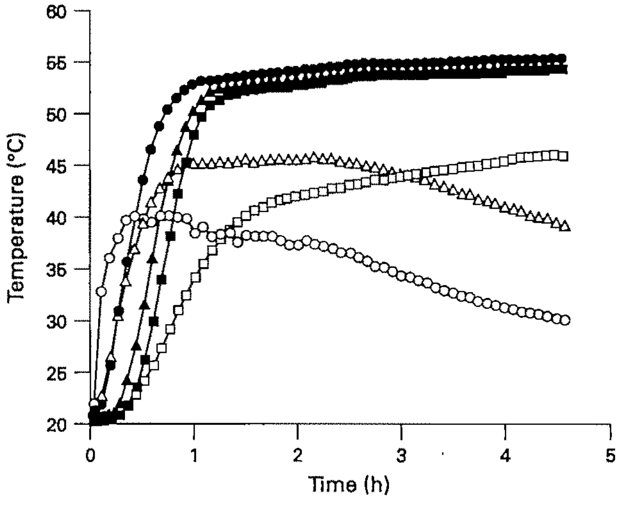

Figure 4 Temperatures at various positions within the upper canister: inlet centre (●), middle centre (▲), outlet centre (■), inlet wall (○), middle wall (△) and outlet wall (□).

Table 1 Summary of compound A studies and predicted near steady-state compound A concentrations. a = Long-term (10 h) study, b = laparoscopic cholecystectomy patients, c = tympanoplasty patients, d = paediatric patients, e = with carbon dioxide 200 ml min^{-1}, f = Baralyme, g = Wakolime-Ace, h = results from Sodasorb and Baralyme combined, i = Wakolime, j = with carbon dioxide 340 ml min^{-1}, k = with carbon dioxide 340 ml min^{-1} and convective cooling, l = with carbon dioxide 340 ml min^{-1} and forced air cooling, m = with carbon dioxide 200 ml min^{-1}, uncooled canister, n = with carbon dioxide 200 ml min^{-1}, canister cooled in ice. NA = not available, NC = not calculable

Research group	Nature of study	Ref.	Sevoflurane (%)	Fresh gas flow (litre min^{-1})	Absorbent (kg)	Temp. (°C)	Compound A found (ppm)	Compound A predicted (ppm)	Difference (predicted–found) (ppm)
1	8 patients	1	2.0	1	2.6	44.6	20	29	9
1	8 patients	1	1.9	3	2.6	37.0	8	6	−2
1	8 patients	1	1.8	6	2.6	29.1	2	2	0
1	8 patients	2	1.08	0.77	2.6	37.8	8	15	7
1	8 patients	2	1.14	0.77	2.6	46.4	20	23	3
2	8 patients	3	1.7	1	2.6	46.0	24	26	2
2	8 patients	3	1.6	1	2.6 (f)	47.0	32	26	−6
2	10 patients (a)	4	1.4	1	2.6	46.3	20	22	2
2	16 patients (b)	5	2.1	1	2.6	46.4	22	33	11
2	8 patients (c)	5	2.1	1	2.6	44.8	20	31	11
3	16 patients	6	2	0.5	2.6	41.6	19	51	32
3	15 patients	6	2	2	2.6	41.5	17	13	−4
1	22 patients (d)	7	2	2	2.6	30.0	5	7	2
2	10 patients	8	2.1	Closed	2.0	46.0	30	NC	NC
4	3 dogs	9	3	0.2	0.7	37.2	21	42	21
4	2 dogs	9	3	0.2	0.7 (g)	37.1	35	41	6
5	Model system (j)	This work	1.5	0.5	1.0	57	29	29	0
5	Model system (k)	This work	1.5	0.5	1.0	51	17	22	−5
5	Model system (l)	This work	1.5	0.5	1.0	42	10	15	−5
6	Model system (m)	10	1.5	0.22	1.2	46	23	50	27
6	Model system (n)	10	1.5	0.22	1.2	26	11	20	9
7	Model system (e)	11	2	0.5	2.4	46.3	28	58	20
7	Model system (e)	11	2	1	2.4 (h)	42.9	23	25	2
7	Model system (e)	11	2	2	2.4 (h)	37.3	15	10	−5
7	Model system (e)	11	2	4	2.6 (h)	27.6	6	3	−3
3	Model system (e)	12	1	0.3	2.6 (h)	44.0	12	47	35
3	Model system (e)	12	2	0.3	2.6	44.0	24	95	71
3	Model system (e)	12	4	0.3	2.6	44.0	41	189	148
8	Model system (e)	13	1	Closed	0.8 (i)	47.9	13	NC	NC
8	Model system (e)	13	2	Closed	0.8 (i)	47.9	30	NC	NC
8	Model system (e)	13	3	Closed	0.8 (i)	47.9	42	NC	NC
8	Model system (e)	14	0.6	Closed	1.6	NA	2	NC	NC
8	Model system (e)	14	1.7	Closed	1.6	NA	5	NC	NC
8	Model system (e)	14	2.7	Closed	1.6	NA	14	NC	NC

volume of water in the absorbent. The effective activation energy can be calculated from:

$$Ea = \frac{-R2.303(\log(k_2) - \log(k_1))}{(\frac{1}{T_2} - \frac{1}{T_1})} \qquad (2)$$

where k_1 and k_2=rate constants at temperatures T_1 and T_2 and R=gas constant. Therefore, by plotting log k against $1/T$ (an Arrhenius plot) for a range of temperatures, the slope of the line provides the net result of all the unknowns in equation (2). When the activation energy is known, and the rate constant at one temperature T_1 is also known, the rate constant at any other temperature T_2 can be determined by rearranging equation (2) and solving for k_2.

Results

The effective rate constant for degradation to compound A was determined at 24 °C with 1 kg of Sodasorb and 18% water, using standard conditions without introduction of carbon dioxide. The near steady-state compound A concentration in the system was then 6 ppm, produced from a reaction volume of 180 ml (18% of 1 kg), a sevoflurane fraction of 0.015 and a fresh gas flow rate of 500 ml min^{-1}. The calculated rate constant from equation (1) was 1.9×10^{-5} s^{-1}.

The temperature dependence of the near steady-state compound A concentration in the breathing system for maximal temperatures of 24–60 °C is presented in the form of an Arrhenius plot in figure 3. The effective activation energy for the formation of compound A, Ea, calculated from the slope of the line in figure 3 using equation (2), is 39 kJ mol^{-1}.

An effective activation energy of 39 kJ mol^{-1} and an effective rate constant of 1.9×10^{-5} s^{-1} at 24 °C were used to calculate (from a rearranged equation (2)) the effective rate constants for the maximum temperatures reported in different studies. Then, equation (1) was used to calculate the predicted near steady-state compound A concentration from the sevoflurane fraction, fresh gas flow rate and amount of absorbent used in the study (assuming a water content of 18%). Studies from eight research groups are summarized in table 1. In some cases mean values for temperature were used. Although not strictly correct mathematically, use of mean values allowed comparison of the studies where temperatures for individual patients were not reported.

A typical temperature profile of the absorbent obtained using the standard conditions with two canisters of Sodasorb is shown in figure 4. Increasing the sevoflurane concentration from 1.5% to 4.0% after 2 h did not change the characteristic shape of the temperature profile (data not shown). Initially, carbon dioxide was absorbed in a narrow carbon dioxide reaction zone at the top of the absorbent. As observed by the change in colour of the pH indicator, this zone moved along the absorbent with time. As shown in figure 4, the maximal temperatures reached at the centre of the canister remained nearly constant with time, indicating efficient heat transfer from the carbon dioxide reaction zone. The wall portions of the absorbent reached temperature maxima at progressively later times, but the combined mean temperature of the wall sites remained approximately constant.

Results from studies performed with commercially available absorbents are shown in table 2. Using 1 kg of Sodasorb in a single canister, maximum concentrations of compound A were in the range 23–41 ppm (mean 29 (SD 5) ppm; n=9) using four different batches of absorbent. Convective cooling of the modified canister gave maximum concentrations of compound A of 15–21 ppm (mean 17 (2.3) ppm; n=5). Forced air cooling of the modified canister gave maximum concentrations of compound A of 9–12 ppm (mean 10 (1.2) ppm; n=6). The predicted and found values are included in table 1.

Results from the fresh gas flow rate study are shown in figure 5. The measured absorbent temperature was approximately constant (46 ± 3 °C) at each flow rate. Increasing the sevoflurane concentration from 1.5% to 4.0% increased mean maximal steady-state concentrations of compound A from 22 to 69 ppm (n=3). The 6 and 8 mesh fractions gave maximum compound A concentrations of 34 ppm and 33 ppm (table 2). In the absorption study, recovery of compound A from the breathing system in the absence of absorbent was 102–114%.

Results from pilot-plant batches of absorbent prepared with different concentrations of sodium and potassium hydroxide are shown in table 3. During initial studies, the lowest concentrations of compound A were observed with about 5% sodium hydroxide, which led to the preparation of a production batch which gave a higher concentration of compound A than any of the pilot-plant batches. The ranges of values observed for both sodium hydroxide batches (9–34 ppm) and potassium hydroxide batches (19–38 ppm) were wide. Correlation of the concentrations of compound A with percentage base was stronger for potassium hydroxide batches (r^2=0.90) than for sodium hydroxide batches (r^2=0.15).

The composition and test results for laboratory batches of absorbent are shown in table 4. Note that the sodium hydroxide and potassium hydroxide types of absorbents were prepared with approximately equal amounts of base on a molar basis.

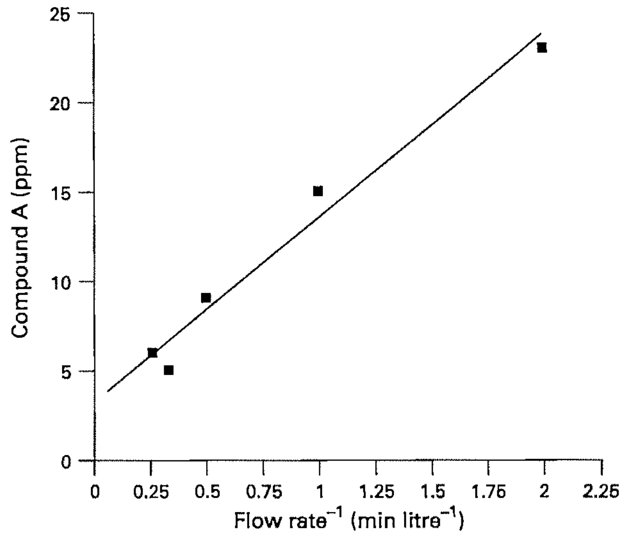

Figure 5 Dependence of near steady-state maximum concentrations of compound A on fresh gas flow rates in a model breathing system. Slope=compound A 10 ppm litre^{-1} min^{-1}; RSD=10%.

Table 2 Maximum temperatures and concentrations of compound A generated with commercial absorbents using standard conditions (see text). * 2 cannisters of 1 kg each

Absorbent	Batch No.	Temperature (°C)	Compound A (ppm)
WR Grace Sodasorb	1	NA	23
WR Grace Sodasorb	1	NA	31
WR Grace Sodasorb	1	NA	29
WR Grace Sodasorb	2	NA	26
WR Grace Sodasorb	2	55	24
WR Grace Sodasorb	2	57	28
WR Grace Sodasorb	2	56	30
WR Grace Sodasorb	3	57	25
WR Grace Sodasorb	4	59	41
WR Grace Sodasorb	4 (6 mesh fraction)	57	34
WR Grace Sodasorb	4 (8 mesh fraction)	56	33
WR Grace Sodasorb	1*	53	19
WR Grace Sodasorb	2*	55	18
WR Grace Sodasorb	2*	58	14
Puritan Bennette Sodalime	1	NA	40
Chemetron Baralyme	1	57	31
Molecular Products Sofnoline GB	1	57	16

Discussion

The temperature profiles within the canister were complex (fig. 4), but attainment of near steady-state concentrations of compound A over long periods of time showed that the effective temperature was relatively constant. Thus an effective activation energy and effective reaction rates could be calculated. Arrhenius plots of near steady-state concentrations of compound A reported in previous studies (plots not shown) gave effective activation energies of 29 kJ mol^{-1} [10], 76 kJ mol^{-1} [11], 55 kJ mol^{-1} [19] and 28 kJ mol^{-1} [13], compared with our value of 39 kJ mol^{-1}.

Values of individual factors used to predict the near steady-state compound A concentrations are shown in table 1; with some exceptions, the predictions agreed with the measured values. Thus in

Table 3 Maximum temperatures and concentrations of compound A generated with pilot-plant batches of absorbent using standard conditions (see text). * Production batch, ** 2 canisters of 1 kg each, *** with convectively cooled canister. NA = not available

Vendor	NaOH (%)	KOH (%)	Temperature (°C)	Compound A (ppm)
1	0.4	0	52	21
1	1.2	0	50	14
1	1.2	0	52	17
1	2.2	0	54	17
1	2.2	0	52	20
1	4.8	0	58	11
1	5.2	0	54	13
1	5.2	0	53	10
1	5.2	0	54	9
1*	5.0	0	57	27
1**	4.8	0	53	12
1***	4.8	0	53	6
2	0	0	NA	17
2	0	0	51	19
2	0	0	53	23
2	1.9	0	55	31
2	3.0	0	56	34
1	0	1.5	52	19
1	0	1.5	54	22
1	0	3.4	54	29
1	0	5.5	58	38
1	0	5.5	55	38
1	0.4	0.7	52	19
1	1.9	0.2	53	17
1	1.5	2.4	55	29

human clinical studies the predicted values are comparable with the measured variables (within +6 to −11 ppm of predicted values), except for the study of 16 patients at site three using a fresh gas flow of 0.5 litre min^{-1}, where a much higher concentration was predicted. However, in clinical practice the entire fresh gas flow is not available to carry compound A out of the breathing system as approximately 80–250 ml min^{-1} of oxygen are converted to carbon dioxide by the patient[5]. If this were corrected for by using a smaller fresh gas flow in equation (1), the predicted concentration would be even higher. In model systems (with no oxygen absorption), the predictions were also much higher than the measured values at fresh gas flow rates of less than 0.5 litre min^{-1}. The steady-state approximation(equation (1)) predicts that as the fresh gas flow rate approaches 0, concentrations of compound A should approach infinity, in contrast with the finite experimental results for closed systems. The most likely explanation for this discrepancy is that a substantial fraction of compound A is degraded during recirculation through the carbon dioxide scrubber. Degradation of compound A in the presence of soda lime has been described[13]; however, insufficient detail exists to calculate the magnitude of removal of compound A from the breathing system by this mechanism. Large non-volatile products could be formed from compound A by repeated additions of methanol and elimination of hydrogen fluoride (an extension of the reaction scheme in fig. 1). Absorption of compound A to the breathing system in the absence of a carbon dioxide absorbent did not appear to be a factor. Further clarification of the degradation of compound A was beyond the scope of our studies.

As described here and elsewhere, results for the individual factors of sevoflurane concentration[12 13], and temperature[10 11 13 19] were in general agreement with the theory. In previous studies, fresh gas flow rate dependence was noted; however, in these studies the temperature varied over a range greater than 15 °C so the true flow rate dependence was not determined[1 11]. However, table 1 sheds no light on the effect of the amount of absorbent on the concentration of compound A because most of the experiments with smaller amounts used fresh gas flows of less than 0.5 litre min^{-1}. The limited data from our own experiments (table 2) tend to contradict the theory showing lower concentrations with larger amounts.

The effective reaction volume may be affected by the moisture content of the absorbent. The surface area of 4–8 mesh absorbent has been estimated as 600 cm^2 cc^{-1}, but only 16% of the area is active in absorbing carbon dioxide because water fills much of the internal pores[20]. The moisture content may change during absorption of carbon dioxide, as the heat of reaction of 1 mol of carbon dioxide (which produces 1 mol, i.e. 18 g of water) is sufficient to vaporize 25 g of water[21]. Measurements of actual vaporization and calorimetry of the system are complex as the heat of reaction is carried away by the recirculating gas, increases the temperature of the soda lime and vaporizes water. The humidity of the recirculating gas should also affect the amount of water vaporized and the increase in temperature in the absorbent. Thus the initial moisture content of the absorbent may significantly affect the sevoflurane degradation reaction volume, and many factors may affect the moisture content and surface area of the

Table 4 Composition of laboratory batchs of absorbent and maximum cincentrations of compound A generated using standard conditions (see text). *Absorbent contained 1.7% polyvinyl alcohol, **remainder is calcium hydroxide

	NaOH type			NaOH and KOH type		KOH type						KOH and $Ba(OH)_2$ type	
% by weight**													
NaOH	3.5	4.2	4.1	2.2	3.3	0	0	0	0	0	0	0	0
KOH	0	0	0	3.1	2.3	6.9	6.8	6.7	6.6	6.4	6.6	4.1	3.5
$Ba(OH)_2$	0	0	0	0	0	0	0	0	0	0	0	9.2	7.9
Glycerol	0.5	1	0	0	1	0	0	0.1	0.5	1	0	0	0.8
Moisture	15	19	21	17	16	15	16	15	16	20	17	24	21
Compound A (ppm)	7	10	14	29	15	38	46	39	31	21	65*	20	17

absorbent during use. Drying Sodasorb from 16% to 11% moisture had little effect on the concentrations of compound A, but drying to 2–6% moisture produced greater concentrations, contrary to the effect of V in equation (1) and different ratios of degradation products[18], suggesting that the chemical mechanism of degradation is dramatically different on a dry surface.

There are contradictory reports on the role of sodium hydroxide, potassium hydroxide and barium hydroxide on the degradation of sevoflurane to compound A [2 3 5 9 13–17]. Significant variability was observed with commercial absorbents (table 2). Pilot-plant batches of absorbent containing 5% sodium hydroxide from vendor 1 (table 3) gave concentrations of compound A which were less than half the concentrations found for Sodasorb. A 5% sodium hydroxide absorbent batch made to production scale by the vendor and pilot-plant batches prepared by a second vendor gave high concentrations of compound A. Pilot-plant batches prepared without either sodium or potassium hydroxide still absorbed carbon dioxide, but with lower efficiency, and produced significant compound A concentrations.

The cause of the variation in compound A concentrations observed with commercial absorbents is unclear (table 2). The variability in size distribution and composition of an absorbent during normal production is low. Thus variability in drying conditions and other manufacturing steps, which may lead to different amounts of reactive surface area, is a more likely explanation. More accurate measurement of the variability of commercial absorbents and clarification of the role of production variables was not pursued.

A chemical approach to scavenge compound A from the breathing system was investigated. An ideal chemical scavenger would be stable and non-volatile in the chemically basic conditions of soda lime or Baralyme, would react with compound A, and form a relatively stable non-volatile product with compound A. The reaction scheme in figure 1 shows that methanol adds across the double bond of compound A to form compound B. Although concentrations of methanol were not measured (fig. 1), low concentrations would be expected as little sevoflurane degrades and the formation of hydrogen from basic solutions of formaldehyde competes with the Cannizarro reaction[22]. Low concentrations of compound B have been detected in breathing systems[3 8 10 13 14]; thus, the nucleophilic addition of methanol readily occurred. Glycerol and polyvinyl alcohol were tested as additives in various calcium hydroxide-based absorbents. As the results in table 4 show, for each type of absorbent tested the concentration of compound A was lower when glycerol was present. These results support the principle of chemical scavenging. The concentrations of compound A with sodium hydroxide-type absorbents were lower than with the potassium hydroxide-type absorbents. Absorbent prepared with polyvinyl alcohol additive gave high concentrations of compound A, possibly because of increased absorption of sevoflurane into the non-polar portion of the polyvinyl alcohol polymer, which effectively increased the contact area with the highly basic absorbent. Results for the Molecular Products Sofnoline GB (table 2), which is not used routinely in breathing systems for general anaesthesia, showed that potassium permanganate used as the indicator may also affect the concentration. Identification of a more reactive additive was not pursued as the maximum concentration of compound A formed in the breathing system appears to be limited by the main factors in the steady-state model, and at low fresh gas flow rates the maximum concentration appears to be limited further by degradation of compound A.

References

1. Bito H, Ikeda K. Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. *British Journal of Anaesthesia* 1995; **74**: 667–669.
2. Frink EJ jr, Malan TP, Morgan SE, Brown EA, Malcomson M, Brown BR jr. Quantification of the degradation products of sevoflurane in two CO_2 absorbants during low-flow anesthesia in surgical patients. *Anesthesiology* 1992; **77**: 1064–1069.
3. Bito H, Ikeda K. Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbents: Quantification of degradation products in the circuit. *Anesthesiology* 1994; **81**: 340–345.
4. Bito H, Ikeda K. Plasma inorganic fluoride and intracircuit degradation product concentrations in long-duration, low-flow sevoflurane anesthesia. *Anesthesia and Analgesia* 1994; **79**: 946–951.
5. Bito H, Ikeda K. Degradation products of sevoflurane during low-flow anaesthesia. *British Journal of Anaesthesia* 1995; **74**: 56–59.
6. Munday IT, Foden ND, Ward PM, van Pelt FNAM, Jones RM. Sevoflurane degradation in a circle system at 2 different fresh gas flow rates. *Anesthesiology* 1994; **81**: A433.
7. Frink EJ jr, Green WB jr, Brown EA, Hammond LC, Valencia FG. Sevoflurane degradation product concentration and hepatorenal function with soda lime in children. *Anesthesiology* 1994; **81**: A366.
8. Bito H, Ikeda K. Closed-circuit anesthesia with sevoflurane in humans. *Anesthesiology* 1994; **80**: 71–76.
9. Suzuki Y, Miyasaka K, Takata M, Nakamura T, Muto R. Concentration of sevoflurane breakdown products with soda lime during 48 hour low-flow anesthesia in dogs. *Anesthesiology* 1994; **81**: A571.
10. Ruzicka JA, Hidalgo JC, Tinker JH, Baker MT. Inhibition of volatile sevoflurane degradation product formation in an anesthesia circuit by a reduction in soda lime temperature. *Anesthesiology* 1994; **81**: 238–244.
11. Fang ZX, Eger EI II. Effect of inflow rate on the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme in a standard anesthetic circuit. Manuscript presented at the public comment portion of the New Drug Application Day for sevoflurane, Rockville, MD, January 17, 1995.
12. Foden ND, van Pelt FNAM, Jones RM. Dose dependent degradation of sevoflurane to compound A. *Anesthesiology* 1994; **81**: A432.
13. Morio M, Fujii K, Satoh N, Imai M, Kawakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, Kumagai Y, Kawai T. Reaction of sevoflurane and its degradation products with soda lime: Toxicity of the byproducts. *Anesthesiology* 1992; **77**: 1155–1164.
14. Hanaki C, Fujii K, Morio M, Tashima T. Decomposition of sevoflurane by sodalime. *Hiroshima Journal of Medical Sciences* 1987; **36**: 61–67.
15. Liu J, Laster MJ, Eger EI II, Taheri S. Absorption and degradation of sevoflurane and isoflurane in a conventional anesthetic circuit. *Anesthesia and Analgesia* 1991; **72**: 785–789.
16. Wong DT, Lerman J. Factors affecting the rate of disappearance of sevoflurane in Baralyme. *Canadian Journal of Anaesthesia* 1992; **39**: 366–369.
17. Strum DP, Eger EI II. Degradation, absorption, and solubility of volatile anesthetics in soda lime depend on water content. *Anesthesia and Analgesia* 1994; **78**: 340–348.
18. Cunningham DD, Webster J, Nelson D, Williamson B. Analysis of sevoflurane degradation products in vapor phase samples. *Journal of Chromatography B: Biomedical Applications* 1995; **668**: 41–52.

19. Strum DP, Johnson BH, Eger EI II. Stability of sevoflurane in soda lime. *Anesthesiology* 1987; **67**: 779–781.
20. Brown ES. The activity and surface area of fresh soda lime. *Anesthesiology* 1958; **19**: 208–212.
21. Brown ES, Bakamjian V, Seniff A. Performance of absorbents: Effect of moisture. *Anesthesiology* 1959; **20**: 613–617.
22. Ashby EC, Doctorovich F, Liotta CL, Neumann HM, Barefield EK, Konda A, Zhang K, Hurley J, Siemer DD. Concerning the formation of hydrogen in nuclear waste. Quantitative generation of hydrogen via a Cannizarro intermediate. *Journal of the American Chemical Society* 1993; **115**: 1171–1173.

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SHORT COMMUNICATION

Evaluation of the usefulness of intrathecal bupivacaine infusion for analgesia after hip and knee arthroplasty

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Summary

Spinal anaesthesia in 47 ASA I–II patients was induced with 0.5% bupivacaine 2 ml via a 28-gauge spinal catheter (L3–4 interspace) and 0.5-ml increments were given if needed before or during hip or knee arthroplasty. Intrathecal 24-h infusions consisted of 0.5% bupivacaine 0.4 ml h^{-1} (2 mg h^{-1}) (n=12), 0.5% bupivacaine 0.2 ml h^{-1} (1 mg h^{-1}) (n=12) or saline (n=11) (12 exclusions). Patients received oxycodone 0.1–0.14 mg kg^{-1} i.m. for rescue analgesia. Infusion of bupivacaine 2 mg h^{-1} provided significantly better postoperative analgesia (19 oxycodone doses per group in 24 h) compared with bupivacaine 1 mg h^{-1} (36 doses of oxycodone per group) and saline (52 doses per group) ($P<0.05$). Five patients in the bupivacaine 2-mg h^{-1} group and none in the other groups had measurable sensory block 24 h after the infusion was started. Three patients in the bupivacaine 2-mg h^{-1} group, two with concomitant arterial hypotension, and one patient in the bupivacaine 1-mg h^{-1} group experienced an increase in block on the ward. The incidence of nausea and vomiting was similar in all groups. Although an effective analgesic, intrathecal infusion of bupivacaine 2 mg h^{-1} cannot be recommended for routine pain relief because of the risk of increasing spinal block. Technical problems (19%) also reduced the overall efficacy of the continuous intrathecal analgesic regimen. (*Br. J. Anaesth.* 1996;**77**:544–545)

Key words

Anaesthetic techniques, subarachnoid. Pain, postoperative. Anaesthetics local, bupivacaine. Surgery, orthopaedic.

Spinal catheter techniques permit flexibility in titrating the extent of spinal anaesthesia and increasing its duration as needed. Spinal catheters can also be used for postoperative pain relief. Opioids are the drugs most often administered intrathecally for postoperative pain[1 2]. However, technical problems with the microcatheters[1–4] and opioid side effects[1 2] are disturbingly frequent.

We decided therefore to evaluate the use of continuous low-dose intrathecal bupivacaine infusion in the treatment of postoperative pain after hip and knee arthroplasty.

Methods and results

The study was approved by the local Ethics Committee and patients gave their verbal informed consent.

We studied 47 ASA I–III patients undergoing hip or knee arthroplasty. All patients were premedicated with oral diazepam 5–15 mg depending on the patient's weight and age. Subarachnoid puncture was performed in the midline at the L3–4 interspace with the patient in the lateral position. A 28-gauge spinal catheter (CoSPAN Kendall, Basingstoke, UK) was inserted via a 22-gauge spinal needle. The catheters were advanced 3–4 cm past the needle tip into the subarachnoid space. Plain 0.5% bupivacaine 2 ml was administered via the catheter and incremental doses of bupivacaine 0.5 ml (maximum four doses=2 ml) were administered with the aim of reaching T6.

Patients were allocated randomly to one of three groups. Patients in group 1 received an intrathecal infusion of plain 0.5% bupivacaine 0.4 ml h^{-1} (2 mg h^{-1}), those in group 2 received 0.5% bupivacaine 0.2 ml h^{-1} (1 mg h^{-1}) and those in group 3 received an intrathecal infusion of saline 0.2 ml h^{-1}. The infusion was given using a syringe pump (JMS Syringe pump SP-100, JMS Company Ltd, Hiroshima, Japan) which was started 60 min after induction of spinal anaesthesia, if the level of spinal block was less than T6. If not, the infusion was started after the block had decreased to less than T6. Increments of bupivacaine 0.5 ml were administered via the catheter during surgery, if needed. All patients had a urinary catheter in place during the study. For postoperative pain (at the operation site), oxycodone 0.1–0.14 mg kg^{-1} i.m. was given on request.

Patients were interviewed by the authors 3, 6, 12 and 24 h after intrathecal infusion was started. Each interview included an assessment of the intensity of pain at rest and on movement of the operated leg using a 20-cm visual analogue scale (VAS) (0–10). Cephalad extension of the sensory and degree of motor block in the lower extremities were recorded. If the spinal block was increasing, the infusion rate was decreased by 50%. Heart rate, arterial pressure, nausea and vomiting were also recorded.

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Table 1 Postoperative 24-h requirement of oxycodone and mean (range) time to first dose in the three intrathecal infusion groups. ** $P < 0.01$ compared with saline

	Bupivacaine 2 mg h^{-1}	Bupivacaine 1 mg h^{-1}	Saline
No. of patients needing oxycodone	7/12	11/12	10/11
No. of doses per group	19**	36	52
No. of doses per patient	1.6 (0–8)	3 (0–9)	4.7 (0–9)
Mean time to first dose (min)	498 (195–940)	408 (30–675)	428 (140–1470)

The spinal catheters were removed by one of the investigators on the first day after operation. For removal, the patient was in the same flexed recumbent position as during spinal puncture.

The Student's *t* test was used for comparison of the differences between mean values for weight, height and age. Fisher's exact test was used for comparison between frequencies. For other data comparisons, the Kruskal–Wallis one-way analysis of variance was applied followed by Dunn's test.

The study was terminated after the 47th patient because of two cases of hypotension related to the reappearance of spinal block during infusion (see below). Twelve patients were excluded from assessment of analgesia, mainly because of technical problems (five accidental disconnections of the catheter, adequate level of spinal analgesia was not reached in three patients and single-dose spinal anaesthesia was given, one failure to insert the catheter and two patients needed intensive care because of haemodynamic instability). One patient wanted the infusion interrupted (bupivacaine 1 mg h^{-1}) because of the disturbing reappearance of sensory and motor block.

Patients receiving bupivacaine 2 mg h^{-1} required significantly less oxycodone (19 doses in 12 patients) than those receiving bupivacaine 1 mg h^{-1} (36 doses in 12 patients) and saline (52 doses in 11 patients) ($P<0.05$). Mean time to administration of i.m. opioid from induction of spinal anaesthesia was comparable in the three groups (table 1). Median VAS scores at 6,12 and 24 h were comparable.

Five patients receiving bupivacaine 2 mg h^{-1} had apparent sensory and motor block 12 h after the infusion was started compared with two patients receiving bupivacaine 1 mg h^{-1} and none receiving saline. Four patients experienced an increase in spinal block on the ward (three in the bupivacaine 2-mg h^{-1} group and one in the bupivacaine 1-mg h^{-1} group). All of these patients also had motor block. The intrathecal infusion was halved at 6.5 h, 8 h and 9.3 h, respectively. Two patients in the bupivacaine 2-mg h^{-1} group developed transient hypotension associated with the increase in block. Five patients in the bupivacaine 2-mg h^{-1} group had detectable sensory block at 24 h. In the bupivacaine groups, of those patients who did not receive any opioid, two of six patients experienced PONV.

Comment

Intrathecal infusion of bupivacaine 2 mg h^{-1} for 24 h provided satisfactory postoperative analgesia in patients undergoing hip or knee arthroplasty. However, because of technical problems, unpredictability of the spread of intrathecal bupivacaine with reappearance of spinal block in some instances, and occasional sudden hypotension, this regimen cannot be recommended as a routine method for postoperative pain relief.

References

1. Niemi L, Pitkänen M, Tuominen M, Rosenberg PH. Comparison of intrathecal fentanyl infusion with morphine infusion or bolus for postoperative pain relief after hip arthroplasty. *Anesthesia and Analgesia* 1993; 77: 126–130.
2. Niemi L, Pitkänen M, Tuominen M, Rosenberg PH. Technical problems and side effects associated with continuous intrathecal or epidural postoperative analgesia in patients undergoing hip arthroplasty. *European Journal of Anaesthesiology* 1994; **11**: 469–474.
3. Pitkänen M, Tuominen M, Rosenberg PH, Wahlström T. Technical and light microscopic comparison of four small-diameter catheters used for continuous spinal anesthesia. *Regional Anesthesia* 1992; 17: 288–291.
4. Silvanto M, Pitkänen M, Tuominen M, Rosenberg PH. Technical problems associated with the use of 32-gauge and 22-gauge spinal catheters. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 295–299.

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CASE REPORTS

Bilateral compartment syndrome complicating prolonged lithotomy position

J. TUCKEY

Summary

A case of bilateral compartment syndrome after prolonged Lloyd-Davies lithotomy position is described. The diagnosis was made early, despite effective extradural bupivacaine–fentanyl analgesia. The aetiology, diagnosis, pathology and treatment of compartment syndrome are described. Complications of the syndrome may be life-threatening and permanently disabling. The anaesthetist should be aware of the potential complications of the operative positions of the unconscious patient. (*Br. J. Anaesth.* 1996;**77**:546–549)

Key words

Position, lithotomy. Position, effects. Complications, compartment syndrome.

The compartment syndrome describes a self-propagating cycle which occurs in the osseofascial compartments of the extremities. After a period of ischaemia, with reperfusion, the integrity of the capillaries may be compromised. This causes interstitial oedema and an increase in compartmental pressure. Untreated, it may lead to permanent neurovascular damage, myoglobinuria, renal failure, sepsis and death[1]. The compartment syndrome may complicate fractures, burns and crush injuries of the extremities[2]. It has also been described as a complication of some positions adopted for surgery, notably the lithotomy and knee–chest positions[3].

Case report

The patient was a 28-yr old man with a 10-yr history of ulcerative colitis. The previous year he had undergone an emergency total colectomy with ileostomy formation for acute exacerbation of the colitis. After colectomy he continued to pass blood and mucus per rectum and did not tolerate the ileostomy. Therefore, he was admitted for formation of an ileal pouch, excision of rectum and pouch–anal anastomosis. He had no other medical conditions of note.

Anaesthesia was induced with thiopentone 3 mg kg^{-1} and fentanyl 2 μg kg^{-1} and neuromuscular block was produced with atracurium 0.5 mg kg^{-1}. The trachea was intubated and the lungs ventilated with 1–2% inspired isoflurane and 35% oxygen in air. An extradural catheter was introduced at the T12–L1 interspace. Extradural analgesia was produced using fentanyl 100 μg and 0.5% bupivacaine 17 ml, with a 3-ml test dose. An extradural infusion of fentanyl 4 μg ml^{-1} and 0.125% bupivacaine was commenced during operation at a rate of 8 ml h^{-1}, 2 h later. Right internal jugular cannulation provided measurement of central venous pressure, and left radial arterial cannulation enabled continuous arterial pressure monitoring.

The patient wore thigh-high anti-embolism stockings and was positioned in the Lloyd-Davies lithotomy position, with the legs well padded and the pressure points protected. For most of the procedure, the table was in the Trendelenburg position. Surgery lasted 7 h 35 min.

Arterial pressure was maintained at or greater than 90/50 mm Hg throughout the procedure. Haemoglobin concentration was maintained greater than 10.2 g dl^{-1} in the peroperative period. Total blood loss was 4.2 litre. The patient's body temperature was 34.5 °C at the end of surgery. He was transferred to the intensive care unit for artificial ventilation of the lungs until his core temperature had returned to normal and fluid status was stable. He was sedated lightly with propofol until the tracheal tube was removed 3 h after operation. By then he was warm, had a stable cardiovascular state and the extradural infusion provided satisfactory analgesia.

The following day, 15 h after operation, with the extradural providing complete abdominal wound analgesia, the patient complained of bilateral painful lower legs. On examination, both lower legs were tense and swollen. The pedal pulses were present and sensation was intact, but the legs were very tender on palpation and pain was elicited on minimal dorsiflexion of the ankle.

No calf muscle pressure monitoring was available. A diagnosis of bilateral compartment syndrome was made clinically. Decompressing fasciotomies were scheduled urgently to minimize the risk of permanent sequelae.

The patient was transferred immediately to theatre. On each side, a 12-cm lateral incision was made under general anaesthesia. Bilaterally, a 3-cm segment of fibula was excised allowing four-compartment decompression. The wounds were left open. The extradural infusion was maintained.

Despite repeated wound inspection under general anaesthesia, on day 4 after operation footdrop was noted. The patient was pyrexic and unwell and so an

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infection screen was carried out. Blood cultures yielded coagulase-negative *Staphylococcus aureus*, and the leg swabs grew coliforms and bacillus. Appropriate antibiotics were given and he was returned to theatre for further leg wound inspection. The extradural had become dislodged and was therefore removed.

On this occasion, large amounts of liquefied muscle were found bilaterally. In the lateral and anterior compartments, extensive areas of necrotic muscle were excised, with blood loss of 4.5 litre. The patient was septicaemic and required cardiovascular support with inotropic agents guided by pulmonary artery catheter studies. Myoglobinuria was detected and creatine kinase concentration peaked at 13 000 iu litre^{-1} on day 5 after the original operation. Urine output was maintained throughout, facilitated by daily infusion of mannitol 0.5 g kg^{-1} and dopamine 3 μg kg^{-1} min^{-1}.

He subsequently required seven additional operations for debridement of wounds and change of dressings during the next 3 weeks. The ankles were splinted to minimize the equinus deformity. The final procedure involved application of split skin grafts to close the wounds.

The abdominal procedure was successful. The patient was discharged 3 months after admission with bilateral foot drop. He could walk short distances with the aid of crutches and ankle supports, after intensive physiotherapy. Despite early diagnosis, the development of compartment syndrome in this patient resulted in significant long-term handicap.

Discussion

Compartment syndrome is defined as a symptom complex that is caused by increased pressure of tissue fluid in a closed osseofascial compartment of the limb and this interferes with circulation to the myoneural components of the compartment[4]. It was first described as a complication of the lithotomy position in a healthy 38-yr old man after urethroplasty lasting 6.5 h[5].

Prolonged lithotomy position may predispose the patient to compartment syndrome in several ways. Leg perfusion may be decreased by elevation of the limb above the heart, excessive local pressure from improper placement of the legs in holders, external pressure from equipment or personnel, or excessive dorsiflexion of the foot. Other intraoperative factors may include hypotension, hypovolaemia, compression of the pelvic blood vessels in association with surgery and hypothermia with vasoconstriction. Initial hypotension on lowering the legs at the end of the procedure may compound the problem. Pre-existing arterial disease may further reduce peripheral perfusion.

Ischaemia results in tissue membrane damage and leads to "leakage" of fluid through capillary and muscle membranes. With arterial reperfusion, the damaged membranes continue to leak and aggravate oedema formation and thus increase the pressure in the closed osseofascial compartment.

It has been shown that at rest the pressure within the calf compartments is normally less than 20 mm Hg[6]. Pressures as high as 50–55 mm Hg for 4–8 h have been cited to result uniformly in compartment syndrome[6]. The patient's baseline arterial pressure must be taken into account. For example, a patient with ankle systolic pressure of 100 mm Hg requires greater occlusion pressures and a longer exposure to these than a patient with peripheral vascular disease with an ankle systolic pressure of 40 mm Hg.

It is important to identify patients at risk of developing compartment syndrome. Patients in the lithotomy position for more than 5 h are at risk[7]. Although the lithotomy position is useful, patients should remain in this position no longer than is necessary.

During a staged operation, repositioning patients during the procedure so that they are in the lithotomy position only when necessary for surgical access should reduce the risk[7]. Care should be taken to ensure correct padding of the extremities. While elevation of the legs above heart level is unavoidable, direct pressure on calf muscles is preventable by using stirrups of the conventional Allen type, where the feet are supported but no pressure is exerted on the muscles of the posterior compartment. In the Lloyd-Davies leg supports, the lower legs rest in cradles, which increase the pressure in the calf muscles.

Irreversible muscle damage is likely to occur with occlusion times greater than 6 h[7]. In those cases in whom prolonged use of the lithotomy position is unavoidable, clinical vigilance is necessary.

Some workers have recommended pulse oximetry of the toes as a monitor of adequate lower limb perfusion during the lithotomy position[1 8]. Others found that the presence of an oximeter signal and a normal saturation reading did not necessarily imply adequacy of tissue perfusion[9]. In the absence of arterial trauma, peripheral pulses are usually present in the compartment syndromes. Pulse oximetry does not appear to be a reliable aid in the diagnosis or monitoring of impaired perfusion caused by increased intra-compartment pressure[10].

Because compartment syndrome is a reperfusion injury, signs and symptoms may not be immediately apparent and may develop insidiously. It develops during the postoperative period where the level of clinical observation may be less intense if the patient is not being nursed in a high dependency area. Residual lower extremity sensory block produced by intraoperative regional block with local anaesthetic may interfere with the early detection of subtle sensory changes. In our patient, and in other reported cases[4 11], effective extradural block did not mask the pain of compartment syndrome.

Urine should be checked for the presence of myoglobin. Serum creatine kinase is increased. The diagnosis of compartment syndrome is essentially clinical. There should be a high index of suspicion in patients at risk. The diagnosis can be confirmed by direct measurement of compartment pressure[12]. It is a simple, although invasive, procedure and therefore there is a risk of introducing infection. The differential diagnoses include deep venous thrombosis and peripheral nerve injury.

The definitive treatment of compartment syndrome is surgical decompression. In our patient, the diagnosis was made early, within 15 h, despite effective extradural analgesia. The fasciotomies must be of sufficient length in all compartments at risk to decompress effectively, and this should be confirmed by direct compartment pressure monitoring. Development of motor neurone signs and loss of pulses are late signs and indicate that irreversible damage has already occurred.

The end result of untreated or inadequately treated compartment syndrome is rhabdomyolysis which has been defined as reversible or irreversible injury of skeletal muscle which alters the integrity of the cell membrane sufficiently to allow escape of cell contents into the extracellular fluid[13]. The association between rhabdomyolysis, myoglobin and acute renal failure was first described during the World War II in patients who had sustained severe muscle injury[14]. Numerous non-traumatic causes of rhabdomyolysis have been described of which compression, alcohol abuse and generalized convulsions are the most common aetiologies[13,15].

Myoglobin is similar in structure to haemoglobin, but smaller and more easily filtered in the kidney. It gives urine a classic red/brown colour. The amount of myoglobinuria does not correlate with the degree of underlying tissue injury[16–18].

The cause of acute renal failure after rhabdomyolysis is multifactorial[19]. It includes intratubular plugging with myoglobin and urate (see below), nephrotoxicity of iron from haem[20,21] which catalyses the formation of oxygen-free radicals and inactivation of the intra-renal nitric oxide vasodilatory influence[19,22], possible associated hypovolaemic or septic shock, hyperphosphataemia and possible tubular blockage from microthrombi secondary to associated disseminated intravascular coagulation.

The biochemical features characteristic of myoglobinuric acute renal failure include hyperphosphataemia, marked hyperuricaemia and severe hypocalcaemia, in addition to increased urea and creatinine concentrations, hyperkalaemia and metabolic acidosis. Hyperuricaemia may be caused by increased production of uric acid in the liver, secondary to increased liberation of adenine nucleotides by damaged muscle[23]. Severe hypocalcaemia may be caused by a combination of marked hyperphosphataemia and skeletal resistance to the calcaemic effect of parathormone in patients with acute renal failure[24]. A transient hypercalcaemia is sometimes seen during the diuretic phase of myoglobinuric acute renal failure. It has been postulated that this phenomenon could be attributed to a transient secondary increase in parathormone, immobilization or remobilization of calcium previously deposited in the damaged muscle[25].

The treatment and prophylaxis of renal failure associated with rhabdomyolysis should commence with cardiovascular resuscitation, where applicable, with aggressive prompt fluid therapy to encourage urine flow. Thereafter, forced alkaline diuresis is beneficial[26,27]. Better suggests a regimen of 12 litre per day of a solution containing sodium 110 mmol litre^{-1}, chloride 70 mmol litre^{-1}, bicarbonate 40 mmol litre^{-1} and mannitol 10 gl^{-1} in 10% glucose[19]. The end-point is to produce diuresis in excess of 8 litre per day, maintaining pH ≥ 6.5. The fluid regimen should be continued until myoglobinuria ceases. Bicarbonate can be discontinued at 36 h. Acetazolamide can be given if arterial pH is ≥ 7.45.

Urate and myoglobin are more soluble in alkaline urine. The renal protective effect of alkalinizing the urine has been demonstrated in animals injected with myoglobin[26,28]. Mannitol also has a beneficial action in the prophylaxis of rhabdomyolysis acute renal failure. The beneficial extra-renal effects include increasing mean arterial pressure[19], increasing cardiac contractility[19,29] and decreasing skeletal muscle oedema, hence decompression of muscle tamponade[30]. The beneficial direct renal effects include a decrease in blood viscosity and oncotic pressure across the glomerulus causing an increase in glomerular filtration rate (GFR), dilatation of glomerular capillaries and stimulation of vasodilatory prostaglandin release, increase in proximal intratubular flow and hence reduction of obstruction, and possible reduction of tubular cell swelling in addition to free radical scavenging[31,32].

References

1. Mulhall JP, Drezner AD. Post-operative compartment syndrome and the lithotomy position: a report of three cases and analysis of potential risk factors. *Connecticut Medicine* 1993; 57: 129–133.
2. Matsen FA, Winquist RA, Krugmire RB. Diagnosis and management of compartmental syndromes. *Journal of Bone and Joint Surgery (American Volume)* 1980; 62: 286–291.
3. Aschoff A, Steiner-Milz H, Steiner HH. Lower limb compartment syndrome following lumbar discectomy in the knee-chest position. *Neurosurgical Review* 1990; 13: 155–159.
4. Montgomery CJ, Ready LB. Epidural opioid analgesia does not obscure diagnosis of compartment syndrome resulting from prolonged lithotomy position. *Anesthesiology* 1991; 75: 541–543.
5. Leff RG, Shapiro SR. Lower extremity complications of the lithotomy position: prevention and management. *Journal of Urology* 1979; 122: 138–139.
6. Mubarak SJ, Hargens AR. Acute compartment syndromes. *Surgical Clinics of North America* 1983; 3: 539–565.
7. Neagle CE, Schaffer JL, Heppenstall RB. Compartment syndrome complicating prolonged use of the lithotomy position. *Surgery* 1991; 110: 566–569.
8. Hovagim AR, Backus WW, Manecke G, Lagasse R, Sidhu U, Poppers PJ. Pulse oximetry and patient positioning : a report of eight cases. *Anesthesiology* 1989; 71: 454–456.
9. Mars M, Hadley GP. Failure of pulse oximetry in the assessment of raised limb intracompartmental pressure. *Injury* 1994; 25: 379–381.
10. Clay NR, Dent CM. Limitations of pulse oximetery to assess limb vascularity. *Journal of Bone and Joint Surgery (British Volume)* 1991; 73: 344.
11. Beerle BJ, Rose RJ. Lower extremity compartment syndrome from prolonged lithotomy position not masked by epidural bupivacaine and fentanyl. *Regional Anesthesia* 1993; 18: 189–190.
12. Moses TA, Kreder KJ, Thrasher JB. Compartment syndrome: an unusual complication of the lithotomy postion. *Urology* 1994; 43: 746–747.
13. Gabow PA, Kaehny WE, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine* 1982; 61; 141–152.
14. Bywaters EGL, Beall D. Crush injuries with impairment of renal function. *British Medical Journal* 1941; 1: 427–432.
15. Rowland LP, Penn AS. Myoglobinuria. *Medical Clinics of North America* 1972; 50: 1233–1256.
16. Paaske WP, Bagl P, Lorentzen JE, Olgaard K. Plasma exchange after revascularization compartment syndrome with acute toxic nephropathy caused by rhabdomyolysis. *Journal of Vascular Surgery* 1988; 7: 757–758.
17. Ratcliffe P, Berman P, Griffith R. Pressure-induced rhabdomyolysis complicating an undiscovered fall. *Age and Ageing* 1983; 12: 245–248.
18. Winterberg B, Tenschert W, Rolf N. Hemofiltration in myoglobinuric acute renal failure. *International Journal of Artificial Organs* 1990; 13: 113–116.
19. Better OS. Post traumatic acute renal failure: pathogenesis and prophylaxis. *Nephrology, Dialysis, Transplantation* 1992; 7: 260–264.
20. Paller MS. Hemoglobin- and myoglobin-induced acute renal failure in rats: role of iron in nephrotoxicity. *American Journal*

of Physiology 1988; **255**: F539–F544.

21. Shah SV, Walker PD. Evidence suggesting a role for hydroxyl radical in glycerol-induced acute renal failure. *American Journal of Physiology* 1988; **255**: F438–F443.
22. Martin W, Villani GM, Jothianandan D, Furchgott RF. Selective blockade of endothelium-dependent and glycerol trinitrate-induced relaxation by hemoglobin and by methylene blue in rabbit aorta. *Journal of Pharmacology and Experimental Therapeutics* 1985; **232**: 708–716.
23. Knochel JP, Dotin LN, Hamburger RJ. Heat stress, exercise and muscle injury: effects on urate metabolism and renal function. *Annals of Internal Medicine* 1974; **81**: 321–328.
24. Massry SG, Arieff AI, Coburn JW. Divalent ion metabolism in patients with acute renal failure. Studies on the mechanism of hypocalcaemia. *Kidney International* 1974; **5**: 437–445.
25. Koffler A, Friedler RM, Massry SG. Acute renal failure due to non-traumatic rhabdomyolysis. *Annals of Internal Medicine* 1976; **85**: 23–28.
26. Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursztein S, Better OS. Prevention of acute renal failure in traumatic rhabdomyolysis. *Archives of Internal Medicine* 1984; **144**: 277–280.
27. Eneas JF, Schoenfeld P, Humphreys MH. The effect of infusion of mannitol–sodium bicarbonate on the clinical course of myoglobinuria. *Archives of Internal Medicine* 1979; **139**: 801–805.
28. Perri GC, Gerini P. Uraemia in the rabbit after injection of crystalline myoglobin. *British Journal of Experimental Pathology* 1952; **33**: 440–444.
29. Better OS, Ben-Haim SA, Edoute Y. Effect of hypertonic mannitol on contractility of isolated working rat heart. *Journal of the American Society of Nephrology* 1990; **1**: 593.
30. Better OS, Zinman C, Reis DN, Har-Shai Y, Rubinstein I, Abassi Z. Hypertonic mannitol ameliorates intracompartmental tamponade in model compartment syndrome in the dog. *Nephron* 1991; **58**: 344–346.
31. Levinsky NG, Bernard DB. Mannitol and loop diuretics in acute renal failure. In: Brenner BM, Lazarus JM, eds. *Acute Renal Failure*, 2nd Edn. New York: Churchill Livingstone, 1988; 841–856.
32. Lazarus JM. Prophylaxis of acute renal failure in the intensive therapy unit. In: Bihari D, Neild G, eds. *Acute Renal Failure in the Intensive Therapy Unit*. London: Springer-Verlag, 1990; 279–309.

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Extradural anaesthesia for Caesarean section in a patient with moyamoya disease

W. D. NGAN KEE AND C. D. GOMERSALL

Summary

We report a case of moyamoya disease in a patient presenting for Caesarean section at 37 weeks' gestation. Extradural anaesthesia was administered using 0.5% bupivacaine and pethidine 25 mg. A stable haemodynamic state was produced using left lateral uterine displacement, i.v. crystalloids and an i.v. infusion of ephedrine. The patient suffered no neurological deficit and there was no significant intraoperative decrease in cerebral oxygenation measured by near infrared spectroscopy. (*Br. J. Anaesth.* 1996;**77**:550–552)

Key words
Anaesthesia, obstetric. Anaesthetic techniques, extradural. Complications, moyamoya disease.

Moyamoya disease is a rare occlusive disease of the large intracranial arteries. Patients are at risk of cerebral ischaemia and haemorrhage, and neurological deterioration may occur during pregnancy. Delivery by Caesarean section has been recommended but the optimal anaesthetic technique is not known and monitoring of cerebral perfusion or oxygenation during anaesthesia has not been described. We report the use of extradural anaesthesia in a term parturient with moyamoya disease, with continuous monitoring of cerebral oxygenation by near infrared spectroscopy.

Case report

The patient, a 36-yr-old, para-1, gravida-4 woman, was admitted at 28 weeks' gestation for observation with a plan for elective Caesarean delivery at 37 weeks' gestation. She had been diagnosed angiographically to have moyamoya disease 4 yr previously after a spontaneous left temporal intracerebral haematoma. Treatment had been conservative and she had made a good recovery with a residual right visual field defect but no other neurological deficit. She had had one normal delivery 13 yr previously. On this admission, there were no abnormal neurological findings other than the visual field defect. Arterial pressure was in the range 100–120/60–80 mm Hg. We planned extradural anaesthesia with invasive haemodynamic monitoring and continuous measurement of cerebral oxygenation by near infrared spectroscopy (NIRS).

The patient remained well for the remainder of the pregnancy, but went into spontaneous labour 4 days before the date of planned surgery and was scheduled to the emergency operating list. She was premedicated with ranitidine 50 mg i.v. and 0.3 mol litre^{-1} sodium citrate 30 ml orally. On arrival in the labour ward, her cervix was 5 cm dilated and pethidine 100 mg i.m. was given for analgesia by the obstetric team. Standard monitoring was applied and 35% oxygen was given by face mask. A radial artery cannula and central venous catheter (via the antecubital fossa) were inserted. Intrathoracic placement of the central venous catheter was confirmed by observation of fluctuations in central venous pressure with respiration. Bifrontal regional cerebral oxygen saturation was measured continuously by NIRS using the Invos 3100 (Somanetics Corp., Troy, MI, USA) and NIRO 500 (Hamamatsu Photonics KK, Hamamatsu City, Japan) (fig. 1). Unfortunately, because the time of operation out of normal hours, there was a delay in preparing the equipment and recordings could only be started after commencement of anaesthesia.

After i.v. preload with lactated Ringer's solution 1000 ml, an extradural catheter was placed in the L2–3 interspace with the patient in the lateral position. She was then turned supine with left lateral tilt. Incremental injections of 3 ml of 0.5% bupivacaine (plain) were given at 4–5-min intervals, followed by pethidine 25 mg via the extradural catheter. I.v. infusion of ephedrine 100–500 μg min^{-1} was titrated throughout the anaesthetic to maintain arterial pressure as near as possible to preoperative values. After 27 ml of bupivacaine, the level of sensory analgesia to pinprick was T6 and surgery was started. A healthy 2.61-kg male infant was delivered with Apgar scores of 9 (1 min) and 10 (5 min). Arterial umbilical cord blood gas tensions were pH 7.294, $P\text{CO}_2$ 6.6 kPa and $P\text{O}_2$ 1.6 kPa, and venous umbilical cord blood gas tensions were pH 7.297, $P\text{CO}_2$ 6.6 kPa and $P\text{O}_2$ 1.8 kPa. Oxytocin 10 u. was given i.v. over 15 min after delivery. Blood loss was approximately 300 ml. A total of 1500 ml of lactated Ringer's solution was given in the perioperative period. To maintain normothermia, all i.v. fluids were warmed, the operating theatre temperature was increased to 22 °C and the patient's upper body was covered with blankets. Continuous temperature monitoring was not available because of technical problems, but the patient's sublingual temperature measured by mercury ther-

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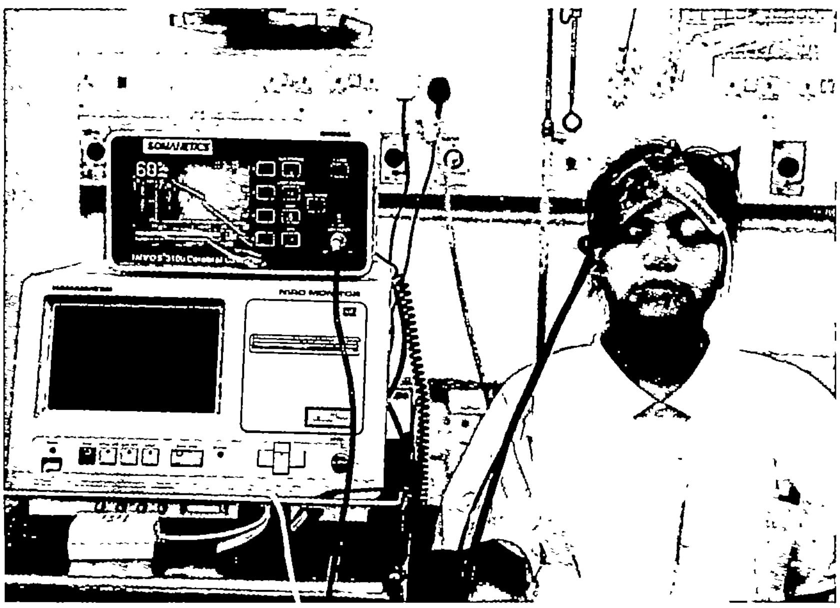

Figure 1 Invos 3100 and NIRO 500 near infrared cerebral oximeters in place on a model.

mometer at the end of the procedure was 36.7 °C. Verbal contact was maintained throughout and bilateral hand grip was checked intermittently. The intraoperative record of arterial pressure, heart rate and cerebral oxygenation is shown in fig. 2. Slight decreases in arterial pressure occurred after establishment of extradural block and after delivery, the latter episode coinciding with administration of oxytocin, but this was not associated with changes in mental state or hand grip and no significant concurrent change in cerebral oxygenation was detected by either spectrometer. A slight increase in deoxyhaemoglobin concentration occurred shortly after skin incision which was matched by an increase in total haemoglobin concentration and no change in cytochrome oxidase redox state.

After operation, the patient was observed in the high dependency area of the labour ward for 24 h where oxygen, pulse oximetry and direct arterial pressure and ECG monitoring were continued. Analgesia was provided by patient-controlled extradural analgesia using pethidine 10 mg ml^{-1} (bolus 20 mg, lockout 10 min). Subsequent progress was uneventful with no new neurological signs and no respiratory depression. The patient was discharged 4 days after delivery.

Discussion

Moyamoya disease is a rare disease named after the Japanese word describing the characteristic "puff of smoke" appearance that is seen on cerebral angiography. It has most often been reported in the Japanese, is more common in children and females and there may be a familial predisposition[1].

Elective Caesarean section has been recommended for the pregnant patient with moyamoya disease to avoid possible deleterious effects of pain, hyperventilation and bearing-down during labour[2]. Although the principles of anaesthesia in moyamoya disease have been described previously[1], the optimal technique during pregnancy is unknown. General anaesthesia has been used[3] and has the potential advantages of decreasing the cerebral metabolic rate for oxygen which may confer some protection against ischaemia[4]. However, there are risks of difficult tracheal intubation, aspiration of stomach contents and neonatal depression. The hypertensive response to intubation may precipitate intracerebral haemorrhage and although this response may be obtunded by the use of adjuvant drugs such as vasodilators, sympathomimetic antagonists and rapidly acting opioids, care must be taken to avoid hypotension and

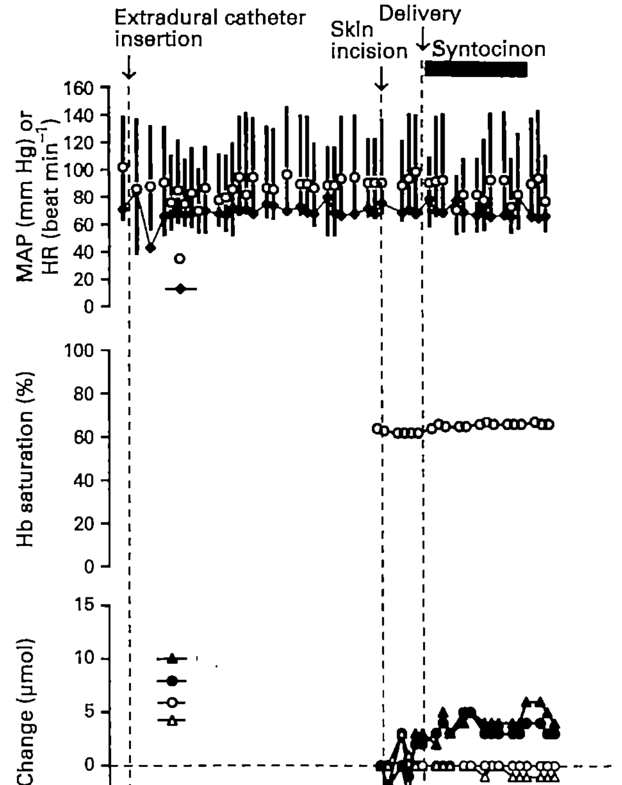

Figure 2 Intraoperative recordings of mean arterial pressure (MAP) (○) and heart rate (HR) (◆) (top), regional cerebral haemoglobin (Hb) saturation measured by the Invos 3100 (middle) and changes in oxyhaemoglobin (▲), total haemoglobin (●), deoxyhaemoglobin (△) and cytochrome oxidase redox state (○) measured by the NIRO 500 (bottom).

consequent cerebral ischaemia. Hypocapnia may cause neurological deficit[5] so use of capnography during controlled ventilation is mandatory. Regional anaesthesia avoids these risks but the associated sympathetic block may lower cerebral perfusion pressure causing ischaemia distal to the stenotic vessels. Spinal anaesthesia was associated with convulsions and hemiparesis in a child[6]. Sharma and colleagues[7] used extradural anaesthesia for Caesarean section in a parturient at 31 weeks' gestation and reported advantages that included continuous monitoring of conscious level and cerebral function in an awake patient. They emphasized the need to avoid hypotension but relied solely on crystalloid preload and uterine displacement to negate the effects of sympathetic block and did not provide details of haemodynamic changes. Because the parturient at term is particularly susceptible to hypotension during extradural anaesthesia[8] more active management may be necessary to maintain cerebral perfusion. However, large upward swings in arterial pressure should also be avoided because of the potential for intracerebral haemorrhage. In our patient we found, using an infusion of ephedrine in addition to fluids and lateral tilt, arterial pressure was well maintained without marked fluctuations.

The absence of signs of cerebral insufficiency in our awake patient in the intraoperative period and the absence of a neurological deficit after operation make it unlikely that significant cerebral ischaemia occurred. However, in the presence of extradural block, signs of transient ischaemia in the anterior cerebral territory may be masked. Anterior cerebral artery occlusion, in the absence of the inconstant recurrent artery of Heubner, leads to flaccid paralysis and cortical sensory loss in the legs, incontinence of urine, and intellectual and memory deficit[9]. However, the level of block required for Caesarean section precludes assessment of neurological function of the legs and bladder. Therefore, we used NIRS to confirm adequacy of oxygenation in the anterior cerebral artery territory.

NIRS uses spectral analysis of reflected infrared light to measure cerebral oxygenation[10]. It has been used to assess cerebral haemoglobin oxygen saturation in both adults[11] and neonates[12], and has been described as a monitor of cerebral oxygenation during carotid endarterectomy[13]. The Invos 3100 gives an absolute value of regional haemoglobin saturation while the NIRO 500 displays changes in regional oxyhaemoglobin, deoxyhaemoglobin, total haemoglobin and cytochrome oxidase redox state. Both monitors are simply and non-invasively applied using probes attached to the patient's forehead. As the maximal distance that can be penetrated by infrared spectrometers is approximately 8 cm[14], the regions of the brain monitored in our patient would have been predominantly within the territory of the anterior cerebral arteries. Although there was a slight increase in deoxyhaemoglobin concentration after skin incision, the concurrent increase in total haemoglobin concentration suggests that any decrease in cerebral oxygenation was likely to be minimal and the absence of a change in cytochrome oxidase redox state shows this did not lead to a change in oxygen delivery at a cellular level.

A disadvantage of using near infrared spectroscopy in emergency surgery is the time required to prepare the equipment: approximately 30 min was required for the lasers of the NIRO 500 to warm up to operating temperature which precluded measurement of cerebral oxygenation before the start of anaesthesia.

Acknowledgement

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References

1. Brown SC, Lam AM. Moyamoya disease—a review of clinical experience and anaesthetic management. *Canadian Journal of Anaesthesia* 1987; **34**: 71–75.
2. Miyakawa I, Lee HC, Haruyama Y, Mori N, Mikura T, Kinoshita K. Occlusive disease of the internal carotid arteries with vascular collaterals (moyamoya disease) in pregnancy. *Archives of Gynecology* 1986; **237**: 175–180.
3. Venkatesh B, Taggart PCM. Anaesthetic management of a patient with Moyamoya disease for Caesarean section. *Canadian Journal of Anaesthesia* 1994; **41**: 79–80.
4. Smith AL, Wollman H. Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. *Anesthesiology* 1972; **36**: 378–400.
5. Sumikawa K, Nagai H. Moyamoya disease and anesthesia. *Anesthesiology* 1983; **58**: 204–205.
6. Yasukawa K, Akagawa S, Nakagawa Y, Miyasaka K. Convulsions and temporary hemiparesis following spinal anesthesia in a child with moyamoya disease. *Anesthesiology* 1988; **69**: 1023.
7. Sharma SK, Wallace DH, Gajraj NM, Willis C, Sidawi E. Epidural anesthesia for a patient with moyamoya disease presenting for cesarean section. *Anesthesia and Analgesia* 1994; **79**: 183–185.
8. Wright RG, Shnider SM. Hypotension and regional anesthesia in obstetrics. In: Shnider SM, Levinson G, eds. *Anesthesia for Obstetrics*. Baltimore: Williams and Wilkins, 1993; 397–406.
9. Patten J. *Neurological Differential Diagnosis*. London: Harold Starke, 1977; 86–98.
10. Harris DNF. Near infra-red spectroscopy. *Anaesthesia* 1995; **50**: 1015–1016.
11. Hampson NB, Camporesi EM, Stolp BW, Moon RE, Shook JE, Griebel JA, Piantadosi CA. Cerebral oxygen availability by NIR spectroscopy during transient hypoxia in humans. *Journal of Applied Physiology* 1990; **69**: 907–913.
12. Wyatt JS. Noninvasive assessment of cerebral oxidative metabolism in the human newborn. *Journal of the Royal College of Physicians of London* 1994; **28**: 126–132.
13. Duncan LA, Ruckley CV, Wildsmith JAW. Cerebral oximetry: a useful monitor during carotid artery surgery. *Anaesthesia* 1995; **50**: 1041–1045.
14. Burcher HU. Detection of cellular hypoxia by monitoring cytochrome oxidase with near infrared spectrophotometry. In: Ehrly AM, Fleckenstein W, Landgraf M, eds. *Clinical Oxygen Pressure Measurement III*. Berlin: Blackwell Wissenschaft, 1992; 15–24.

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Unrecognized "crack" cocaine abuse in pregnancy

D. CAMPBELL, M. J. A. PARR AND L. E. SHUTT

Summary

We report a case of "crack" cocaine abuse in a pregnant patient associated with haematuria, proteinuria, haemolytic anaemia, renal impairment, thrombocytopenia and pulmonary oedema. The case illustrates the problems for clinicians where unrecognized cocaine abuse interferes with the diagnosis and management of a complicated pregnancy. In addition, we discuss the principles for the safe conduct of anaesthesia in the pregnant cocaine abuser. (*Br. J. Anaesth.* 1996;**77**:553–555)

Key words

Anaesthesia, obstetric. Complications, cocaine abuse. Pregnancy.

"Crack" cocaine abuse in pregnancy is well recognized in the USA. In the UK the level of awareness to this increasingly common problem needs to be improved[1]. This case illustrates the difficulties in differentiating the effects of cocaine abuse from the more usual complications of pregnancy. Cocaine has complex effects on many systems. It was not apparent until post-partum that the patient continued to abuse crack cocaine even while an inpatient. In retrospect the relationship between drug abuse and the course of her illness became clear.

Crack cocaine abuse increases maternal morbidity, fetal morbidity and death[2-4]. It is likely that maternal crack cocaine abuse will be an increasing problem in the UK and at present the clinical effects may not be fully recognized.

Case report

A 32-yr old, gravida 5, para 3, Afro-Caribbean woman presented to her general practitioner for antenatal assessment at 10 weeks' gestation. Her haemoglobin concentration was 10.1 g dl^{-1} and the blood film showed macrocytosis. Cervical and high vaginal swabs were infected with *Gonococcus* and *Trichomonas*. Her infection was treated and she attended again at 19 weeks' gestation when urinalysis showed moderate haematuria and mild proteinuria. Arterial pressure was 120/70 mm Hg.

She did not attend again until 31 weeks' gestation when she complained of fatigue and dyspnoea on exercise. On physical examination her conjunctivae were pale, arterial pressure was 125/70 mm Hg and she had bilateral pitting oedema of the ankles. Cardiovascular and respiratory system examinations were otherwise unremarkable. Abdominal examination was consistent with a 31-week pregnancy with normal fetal heart sounds and movements. Urinalysis showed excessive blood and moderate protein. The full blood count result a week later showed haemoglobin 6.8 g dl^{-1}, mean cell volume 110 fl and platelets 63×10^9 $litre^{-1}$, and therefore hospital admission was arranged.

In hospital, physical examination revealed an apical ejection systolic murmur. Deep tendon reflexes were normal. Her blood film showed a reticulocyte count of 4.9%. Serum creatinine concentration was 99 mmol $litre^{-1}$, which is high for a pregnant patient. Urea and electrolyte concentrations, liver function tests, uric acid and clotting screen were within normal limits. Autoimmune profile, lupus and platelet antibodies and haemosiderin were within normal limits but haptoglobin concentrations were low at 0.2 g $litre^{-1}$. The 24-h urine volume was 2125 ml and protein 1.32 g $litre^{-1}$. Creatinine clearance was impaired at 90 ml min^{-1}. Free haemoglobin concentration was detected in urine. She was treated with folic acid 10 mg orally twice daily and transfused with 2 u. of packed red blood cells.

A bone marrow aspirate was performed and showed some megakaryocytes and a microangiopathic picture. Later the same day she became hypertensive with an arterial pressure of 145/95 mm Hg which decreased with bed rest alone. The patient admitted also to a history of smoking crack cocaine for the past year. At this stage the differential diagnoses being considered were pre-eclampsia, haematological illness related to renal disease or pregnancy, such as haemolytic–uraemic syndrome, or renal disease, probably secondary to drug abuse.

Additional blood transfusions were given over the next 2 days; haemoglobin concentration was then 9.3 g dl^{-1}. On day 4 of admission she left the ward for the afternoon and on her return she had a dry cough, left-sided pleuritic chest pain, shivering, temperature of 37.5 °C, heart rate 110 beat min^{-1}, arterial pressure 140/80 mm Hg, ventilatory frequency 34 bpm and

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crackles on auscultation of the chest. Blood cultures were obtained, oxygen was given by face mask and antibiotic therapy with Augmentin was started. The next morning the patient had another episode of breathlessness thought to be caused by fluid overload. ECG was normal but a chest x-ray showed cardiomegaly and pulmonary oedema. Frusemide 20 mg i.v. produced improvement. However, an echocardiogram showed tachycardia, hyperdynamic left ventricle, ejection fraction of 62%, small pericardial effusion and mild tricuspid regurgitation.

There was an additional episode of breathlessness the next morning and a decision to expedite delivery was made. It was felt that she would not tolerate vaginal delivery and a Caesarean section was planned. The preoperative anaesthetic assessment noted the history of crack cocaine abuse, hepatitis B positive, high risk for HIV infection and the need for appropriate precautions. Despite the uncertainty of the diagnosis there was some comfort in the patient having a normal arterial pressure, no clinical evidence of heart failure, haemoglobin 9.7 g dl^{-1}, and normal urea and creatinine concentrations, and clotting screen. As the platelet count was 60×10^9 $litre^{-1}$, arrangements were made for a platelet transfusion of 12 u. before surgery.

The patient was premedicated with ranitidine 50 mg i.v. and sodium citrate 0.3 mol $litre^{-1}$ (30 ml) orally before induction of anaesthesia. After local anaesthesia of the skin, cannulae were inserted via the right brachial artery and right internal jugular vein for monitoring of arterial pressure and central venous pressure. Her lungs were preoxygenated for 5 min and this was followed by rapid sequence i.v. induction with etomidate 20 mg, suxamethonium 100 mg and alfentanil 1 mg, and application of cricoid pressure. Anaesthesia was maintained with 1% isoflurane and 50% nitrous oxide in oxygen. Fourteen minutes later a live male neonate, weighing 2.07 kg with Apgar scores of 6 and 8, was delivered. Synthetic oxytocin (Syntocinon) 7.5 u., fentanyl 100 µg, vecuronium 6 mg and Augmentin 1.2 g were given i.v. The patient remained haemodynamically stable throughout and her trachea was extubated at the end of the procedure. The patient was monitored for a further 24 h in the intensive care unit. Pain was managed by intermittent i.v. boluses of morphine for 24 h and oral analgesia thereafter. The only problem was some oozing from the abdominal wound.

After operation a more discerning drug history was obtained. The patient had been smoking crack cocaine on hospital premises immediately before each episode of dyspnoea and this was thought to precipitate the presumed episodes of acute pulmonary oedema. Urine toxicology confirmed the presence of cocaine metabolites in urine.

The patient was discharged home 9 days after operation. A renal biopsy before discharge showed glomerular immune complex deposits (M dominant) on immunohistology and evidence of intraglomerular intravascular coagulation with some features of haemolytic–uraemic syndrome on electron microscopy. These findings are consistent with the mixed renal disease found in drug abuse. Additional blood investigations showed a haemoglobin concentration of 9.8 g dl^{-1}, platelets 120×10^9 $litre^{-1}$ and serum creatinine concentration 130 mmol $litre^{-1}$. Follow-up of her suspected drug-induced haemolytic–uraemic syndrome by a renal physician was planned.

Discussion

Cocaine is an alkaloid derived from the shrub *Erythroxylon coca* and is available as a hydrochloride or free base crack cocaine. Cocaine hydrochloride is usually "snorted" achieving peak plasma concentrations in less than 15 min. Crack cocaine is smoked and produces euphoria in less than 1 min with a duration of only 5–10 min[5 6].

The effect of cocaine as a local anaesthetic is a result of its action on sodium channels preventing nerve depolarization. The systemic effects of cocaine are caused by block of reuptake of noradrenaline and dopamine from synapses in the central and sympathetic nervous systems thereby potentiating the effects of these neurotransmitters. The euphoric effect of cocaine is caused by excess neurotransmitters at the synapses of the limbic system. Sympathetic nervous system effects include vasoconstriction, tachycardia, hypertension and arrhythmias. Chronic abuse causes tachyphylaxis resulting from depletion of presynaptic neurotransmitters[7 8].

Our patient had features in common with other reports[3 7], including a poor socioeconomic background and infrequent attendance for antenatal care. The paroxysmal dyspnoea was related to pulmonary oedema associated with acute intoxication after smoking crack cocaine. This has been described previously[9 10] in the non-obstetric population and may reflect transient left ventricular dysfunction or a direct pulmonary microcirculatory effect.

Cocaine abuse can be confused with pre-eclampsia[11] in its presentation. In this case hypertension was not a prominent feature although the patient did have proteinuria, ankle oedema and thrombocytopenia. Haemolysis has been reported rarely and only as haemolytic–uraemic syndrome associated with cocaine abuse[12]. Thrombocytopenia is well described[13]. Many cardiovascular complications are reported[14] but we can find no evidence of pericardial effusion associated with cocaine abuse.

The routine questioning of patients about recreational drug use should become standard in our preoperative assessment. Where cocaine is implicated, non-emergency surgery should be delayed until signs of acute cocaine intoxication have disappeared. This may not be possible in obstetric patients where acute cocaine intoxication may cause fetal distress or placental abruption[2 5]. Propranolol has been used for the control of acute hypertension in cocaine intoxication but may increase hypertension and coronary vasoconstriction because of unopposed α adrenoceptor stimulation[15]. For this reason labetalol[16], which antagonizes α and β adrenergic receptors, and esmolol[17], the short-acting β_1 selective antagonist, may be more appropriate agents to use. Hydralazine controls hypertension but does not restore uterine blood flow[18]. Arrhythmias are best treated with the β adrenoceptor antagonists labetalol or esmolol. Cocaine lowers the seizure threshold and therefore lignocaine is contraindicated. Nifedipine has been shown to be protective for cardiovascular side effects in animal models of cocaine toxicity only if given before cocaine[19]. Calcium antagonists have also been associated with increased mortality during cocaine intoxication in animals but there is no evidence in humans[20]. Diazepam is the drug of choice for controlling seizures in acute cocaine intoxication but barbiturates may be necessary[21]. Other systemic complications of acute cocaine intoxication are best managed by waiting for the acute cocaine intoxication to wear off.

Regional anaesthesia is possible in cocaine abusing obstetric patients but is associated with several pitfalls. Regional anaesthesia requires a relaxed cooperative patient which may not be the case in acute intoxication. The cocaine abusing patient may suffer vasoconstriction and have a reduced circulating blood volume which would make extradural anaesthesia preferable to spinal anaesthesia. The interaction of cocaine with other local anaesthetics makes the calculation of a safe maximum dose difficult. Thrombocytopenia is common in the chronic cocaine abusing patient[13] and may be a contraindication to regional anaesthesia.

Where it is not possible to delay surgery in the acutely cocaine intoxicated patient, selected balanced general anaesthesia seems to be without risk. No specific induction agent is recommended but thiopentone and etomidate have been suggested as suitable for induction of anaesthesia[7]. Ketamine increases the risk of cocaine-associated arrhythmias[22]. Alfentanil has been used to prevent the hypertensive response to laryngoscopy and intubation in patients undergoing general anaesthesia for Caesarean section[23]. For hypertensive disorders of pregnancy, many agents have been used to attenuate the cardiovascular response to laryngoscopy, including labetolol, alfentanil and fentanyl[24]. These agents appear to be safe in the context of acute cocaine intoxication.

Halothane increases the chance of arrhythmias with cocaine[21]. Isoflurane anaesthesia preserved blood flow to most major organs but also increased the incidence of arrhythmias in a swine model of acute cocaine toxicity[25]. It is theoretically possible that indirectly acting vasoconstrictors such as ephedrine may be less effective in chronic cocaine abusers because of neurotransmitter depletion from nerve terminals[5]. More dangerous is the interaction between cocaine and direct-acting sympathomimetics causing tachycardia, hypertension, left ventricular failure and pulmonary oedema[21 26].

In conclusion, we have reported a case in which crack cocaine abuse was associated with major complications during pregnancy. In the light of evidence of increasing drug abuse, we encourage anaesthetists to be aware of the pathophysiological effects of acute cocaine intoxication and the multiple organ involvement observed in chronic abuse.

References

1. Morrison C, Sincy C. Maternity services for drug misusers in England and Wales: a national survey. *Health Trends* 1995; 27: 15–17.
2. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstetrics and Gynecology* 1992; 79: 778–789.
3. Nair BS, Watson RR. Cocaine and the pregnant woman. *Journal of Reproductive Medicine* 1991; 36: 862–867.
4. Spence MR, Williams R, DiGregorio GJ, Kirby-McDonnell A, Polansky M. The relationship between recent cocaine use and pregnancy outcome. *Obstetrics and Gynecology* 1991; 78: 326–329.
5. Kain ZN, Rimar S, Barash PG. Cocaine abuse in the parturient and effects on the fetus and neonate. *Anesthesia and Analgesia* 1993; 77: 835–845.
6. Cheng D. Perioperative care of the cocaine abusing patient. *Canadian Journal of Anaesthesia* 1994; 41: 883–887.
7. Baysinger CL, Schultetus RR. Cocaine abuse during pregnancy: effects on mother and child. *Current Opinion in Anesthesiology* 1990; 3: 418–422.
8. Volpe JJ. Effect of cocaine use on the fetus. *New England Journal of Medicine* 1992; 327: 399–407.
9. Kline JN, Hirasuna JD. Pulmonary edema after freebase cocaine smoking–not due to an adulterant. *Chest* 1990; 97: 1009–1010.
10. Hoffman CK, Goodman PC. Pulmonary edema in cocaine smokers. *Radiology* 1989; 172: 463–465.
11. Towers CV, Pircon RA, Nageotte MP, Porto M, Garite TJ. Cocaine intoxication presenting as pre-eclampsia and eclampsia. *Obstetrics and Gynecology* 1993; 81: 545–547.
12. Ito K, Komatsu Y. Drug induced haemolytic uraemic syndrome. *Nippon Rinsho* 1993; 51: 204–209.
13. Burday MJ, Martin SE. Cocaine associated thrombocytopenia. *American Journal of Medicine* 1991; 91: 656–660.
14. Cregler LL. Cocaine: the newest risk factor for cardiovascular disease. *Clinical Cardiology* 1991; 14: 449–456.
15. Lange RA, Cigarroa RG, Flores ED, McBride W, Kim AS, Wells PJ, Bedotto JB, Danziger RS, Hillis LD. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Annals of Internal Medicine* 1990; 112: 897–903.
16. Gay GR, Loper KA. The use of labetolol in the management of cocaine crisis. *Annals of Emergency Medicine* 1988; 17: 282–283.
17. Pollan S, Tadjziechy M. Esmolol in the management of epinephrine- and cocaine-induced cardiovascular toxicity. *Anesthesia and Analgesia* 1989; 69: 663–664.
18. Vertommen JD, Hughes SC, Rosen MA, Shnider SM, Espinoza MI, Messer CP, Johnson JL, Parer JT. Hydralazine does not restore uterine blood flow during cocaine-induced hypertension in the pregnant ewe. *Anesthesiology* 1992; 76: 580–587.
19. Hale SL, Alkes KJ, Rezkalla SH, Eisenhauer AC, Kloner RA. Nifedipine protects the heart from the acute deleterious effects of cocaine if administered before but not after cocaine. *Circulation* 1991; 83: 1437–1443.
20. Derlet RW, Albertson TE. Potentiation of cocaine toxicity with calcium channel blockers. *American Journal of Emergency Medicine* 1989; 7: 464–468.
21. Fleming JA, Byck R, Barash PG. Pharmacology and therapeutic applications of cocaine. *Anesthesiology* 1990; 73: 518–531.
22. Koehntop DE, Liao JC, Van Bergen FH. Effects of pharmacologic alterations of adrenergic mechanisms by cocaine, topolone, aminophylline and ketamine on epinephrine-induced arrhythmias during halothane–nitrous oxide anesthesia. *Anesthesiology* 1977; 46: 83–93.
23. Dann WL, Hutchinson A, Cartwright DP. Maternal and neonatal responses to alfentanil administered before induction of general anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1987; 59: 1392–1396.
24. Mushambi MC, Halligan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. *British Journal of Anaesthesia* 1996; 76: 133–1348.
25. Boylan J, Cheng DCH, Sandler AN, Feindel C, Carmichael F, Boylan P. Cocaine–isoflurane interaction in swine: regional blood flow effects. *Anesthesia and Analgesia* 1993; 76: S26.
26. Singh PP, Dimich I, Shamsi A. Intraoperative pulmonary oedema in a young cocaine smoker. *Canadian Journal of Anaesthesia* 1994; 41: 961–964.

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Heparinase-guided thrombelastography in an anticoagulated parturient

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Summary

We describe the use of heparinase-guided thrombelastography in the assessment of a parturient who had been anticoagulated with heparin for suspected thromboembolic disease. Reversal of the heparin effect in the heparinase-treated sample facilitated administration of protamine and successful subarachnoid analgesia for delivery. (*Br. J. Anaesth.* 1996;**77**:556–558)

Key words

Anaesthetic techniques, subarachnoid. Blood, anticoagulants, heparin. Measurement techniques, thrombelastography.

Case report

A 35-yr-old gravid 1 para 0 presented at 29 weeks' gestation with right upper extremity weakness, scintillating scotomata of her right visual fields and drooping of her left facial muscles. She had a significant smoking history and family history of paternal cerebrovascular accident (CVA) at 27 yr of age, followed by three further CVA and death from myocardial infarction at 46 yr. Her sister, 32 yr, had recently had a CVA with documentation of an abnormal mitral valve.

Magnetic resonance imaging (MRI) revealed an ischaemic injury in the distribution of the right middle cerebral artery without evidence of cortical venous or sinus thrombosis. Prothrombin time (PT) was 12.4 s (normal 10.5–13 s) and accelerated partial thromboplastin time (aPTT) was 29.9 s (normal 25–34 s). Heparin 1500 u. h^{-1} was started i.v. and her aPTT was 70 s before transfer to our hospital.

On admission, the fetus was active and the patient was not in labour. History and examination were otherwise unremarkable. Transoesophageal echocardiography (TEE), performed to elucidate a possible thromboembolic source, demonstrated an 8-mm mobile mass on both mitral valve leaflets. Magnetic resonance angiography (MRA) revealed right middle cerebral artery occlusion suggestive of embolic origin.

Carotid arteriogram, 24-h Holter monitoring and lower extremity Doppler examination for venous thrombosis were negative. Serial blood cultures were negative for infection, as were tests for connective tissue disorders and homocysteinuria. Although protein C concentrations were normal, functional protein S was reduced at <10% (normal 65–140%), but total and free protein S fractions were normal. The test for functional protein S was repeated and a more appropriate result of 116% was obtained. Activated protein C resistance testing was negative. Serum cholesterol concentration was marginally increased and triglycerides were twice normal. Haematological variables, including antithrombin III and D-dimers, were normal.

As the patient had no biochemically definable coagulopathy present, a presumptive diagnosis of familial valvulopathy was made. Heparin was infused i.v. for 5 days to maintain an aPTT of 50–80 s, followed by heparin 2000 u. h^{-1} s.c. which was continued for the duration of her confinement.

The patient was readmitted 3 months later, at 39 weeks' gestation, for planned induction of labour. Repeat echocardiography revealed no masses on her mitral valve. Her aPTT on admission was >100 s. Heparin was discontinued 8 h before the intended placement of an extradural catheter for analgesia during labour. Nine hours later prothrombin time (PT) was 13.0 s (normal 11.1–13.1 s), packed cell volume 33.6% and platelet count 154 000 ml^{-1} (normal 133 000–333 000 ml^{-1}). However, aPTT was prolonged at 84.5 s (normal 25–34 s). Thrombelastography (TEG) with native blood (fig. 1A) confirmed a heparin-like effect, evidenced as a prolonged *r* (reaction) time, prolonged *k* time and decreased angle (suggesting poor clot formation), and a narrow maximum amplitude (MA), implying poor platelet function. Simultaneously, a TEG was performed on a heparinase-treated sample (fig. 1B), which revealed a normal trace.

The demonstrated heparin effect was then reversed *in vivo* with protamine 50 mg, given slowly i.v. The repeat TEG trace after protamine was normal (fig. 2), although the aPTT remained prolonged at 46.1 s.

As labour had begun with the fetus in the occipito-posterior position and considerable maternal discomfort, regional anaesthesia was considered desirable. With TEG evidence of adequate coagulation,

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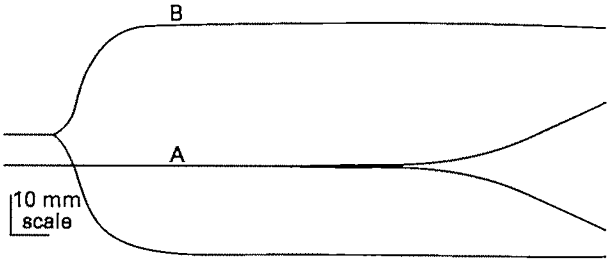
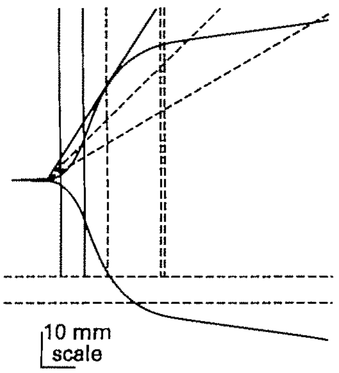


		SP (mm)	r (mm)	k (mm)	MA (mm)	Angle (°)
B	Pt:	17.0	19.5	4.5	77.0	62.0
	NR:		39–40	0–13	48–60	29–43
A	Pt:	67.	124.0	58.5	(58.5)	(9.5)
	NR:	0	39–40	0–13	48–60	29–43

Figure 1 Thrombelastograph traces before administration of protamine for native whole blood (A) and native whole blood with heparinase (B). Pt=patient measurements, NR=normal range. SP=split point (mm)—each mm represents 30 s. It is defined as the time from sample placement to first divergence of the trace; *r* (mm)=reaction time (time from sample insertion to 2 mm separation of trace); *k* (mm)=time from 2 mm trace separation to 20 mm trace separation; MA (mm)=maximum amplitude, maximum width of the trace; Ang (°)=clot formation rate (angle formed by the upslope of the TEG tracing from the *r* value).



	SP (mm)	r (mm)	k (mm)	MA (mm)	Angle (°)
Pt:	9.0	12.0	6.5	88.5	55.5
NR:		39–40	0–13	48–60	29–43

Figure 2 Thrombelastograph trace after administration of protamine. Abbreviations as in figure 1.

sufentanil 10 µg and bupivacaine 2.5 mg were given into the subarachnoid space via a 27-gauge Whitacre needle by an experienced operator (E. A.) at the first attempt. Analgesia was effective, labour progressed rapidly, and a healthy 3.8-kg female was delivered with low forceps 1 h after intrathecal drug administration.

Post-partum TEG (1 h after delivery) showed no evidence of coagulopathy, heparin therapy was recommenced, and mother and child were discharged 3 days later with planned haematology follow-up for management of maternal warfarin.

Discussion

This report describes several issues in the preoperative haematological management and assessment of obstetric patients for regional anaesthesia.

Heparin is the currently favoured agent for anticoagulation in the parturient[1]. This patient with suspected thromboembolic disease required substantial doses (2000 u. h^{-1} s.c.) for optimal effect, as measured by aPTT. Although a lower dose of unfractionated s.c. heparin has a half-life of 3–4 h[2], the anticoagulant response of heparin increases disproportionately at increased doses[3]. In our patient, a minimum of 8 h was anticipated to allow for waning of the anticoagulant effect before proposed extradural catheter insertion. However, 9 h after discontinuation, the prolonged aPTT suggested a heparin effect. Monitoring of the clinical heparin effect using the activated clotting time may be unreliable (in the presence of low heparin doses)[4], and not representative of *in vivo* activity with plasma heparin concentrations. As heparinase-guided thrombelastography has been introduced into cardiac surgery[5] and orthotopic liver transplantation, we used this method to assist clinical decision making in this patient.

Thrombelastography is enjoying widespread use in obstetrics. While value ranges for healthy parturients have not corresponded, they have all tended towards hypercoagulability compared with healthy non-pregnant patients[6 7]. Investigation continues into TEG changes during preeclampsia[8] and the HELLP syndrome, and the TEG is useful in the algorithm for the thrombocytopenic patient requiring assessment for extradural analgesia. The availability of heparinase, isolated from *Flavobacterium heparinum*[9], further extends the usefulness of this test, as the enzyme degrades heparin and heparin-like linkages even in the presence of the large doses of heparin required for cardiopulmonary bypass[5].

The native TEG trace in this patient showed marked prolongation of the *r* and *k* times and a narrow angle and MA, compatible with a heparin effect. Addition of heparinase to the sample restored the trace to that of the typical parturient. With this evidence of a heparin effect, systemic administration of protamine to the patient was followed by return to normal of the native trace.

Although safe neuraxial access has been described in anticoagulated patients[10], correction of the anticoagulation in this patient (in the presence of normal platelet number and function) significantly improved the risk–benefit ratio of regional analgesia. As labour was progressing adequately, it was felt that single-shot spinal analgesia would provide the necessary analgesia for completion of the second stage of labour without the risk of an indwelling extradural catheter. The addition of bupivacaine 2.5 mg to sufentanil 10 µg prolongs subarachnoid analgesia[11 12]. The normal TEG trace obtained with native blood 1 h post-partum was further assurance that there was no significant (if any) release of heparin from the s.c. tissues after administration of protamine.

References

1. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clinical Pharmacokinetics* 1992; **22**: 359–374.
2. de Swart CAM, Nijmeyer B, Roelofs JMM, Sixma JJ. Kinetics of intravenously administered heparin in normal humans. *Blood* 1982; **60**: 1251–1258.
3. Bara L, Billaud E, Kher E, Samama M. Increased anti-Xa bioavailablity for a low molecular weight heparin (PK 10169) compared with unfractionated heparin. *Seminars in Thrombosis and Hemostasis* 1985; **11**: 316–317.
4. Aren C. Heparin and protamine during cardiac surgery. *Perfusion* 1989; **4**: 171–181.
5. Tuman KJ, McCarthy RJ, Djuric M, Rizzo V, Ivankovich AD. Evaluation of coagulation during cardiopulmonary bypass

with a heparinase-modified thromboelastographic assay. *Journal of Cardiothoracic and Vascular Anesthesia* 1994; **8**: 144–149.

6. Steer PL, Krantz HB. Thromboelastography and Sonoclot analysis in the healthy parturient. *Journal of Clinical Anesthesia* 1993; 5: 419–424.
7. Wong CA, Liu S, Glassenburg R. Comparison of thromboelastography with common coagulation tests in preeclamptic and healthy parturients. *Regional Anesthesia* 1995; **20**: 521–527.
8. Payne AJ, Orlikowski CEP, Moodley J, Rocke DA. Thromboelastography as a measure of coagulation in high risk pregnant patients receiving low dose aspirin. *Journal of Obstetrics and Gynaecology* 1993; **113**: 222–226.
9. Klein MD, Drongowski RA, Linhardt RJ, Cooney CL, Langer RS. Heparinase: In vivo activity and immunogenicity in rabbits. *Journal of Laboratory and Clinical Medicine* 1983; **102**: 828–837.
10. Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy: experience with one thousand cases of continuous epidurals. *Anaesthesia* 1983; **38**: 254–259.
11. Abouleish A, Abouleish E, Camann W. Combined spinal–epidural analgesia in advanced labour. *Canadian Journal of Anaesthesia* 1994; **41**: 575–578.
12. Campbell DC, Camann WR, Datta S. The addition of bupivacaine to intrathecal sufentanil for labor analgesia. *Anesthesia and Analgesia* 1995; **81**: 305–309.

British Journal of Anaesthesia 1996;77:559–562

CORRESPONDENCE

Failed tracheal intubation

Sir,—I read with interest the article by Hawthorne and colleagues detailing failed intubations over 17 yr in a teaching maternity unit[1]. One result reported was that in only one of seven failed intubations for Caesarean section for fetal distress was neonatal outcome poor. In that instance it was thought that antepartum factors rather than the delay in delivery may have been responsible. Good neonatal outcome despite the considerable delays in delivery that would have occurred in these cases raises the question of the value, if any, of providing general, rather than regional, anaesthesia to expedite Caesarean section for fetal distress.

As discussed by Hawthorne and colleagues, general anaesthesia is a potential cause of maternal morbidity and mortality[2 3]. It also causes increased neonatal respiratory depression and the need for active resuscitation[4]. Regional anaesthesia may take longer to establish, but this delay does not necessarily cause neonatal morbidity even when the indication for surgery is fetal distress. A study of 212 emergency Caesarean sections by Quinn and Kilpatrick found that the use of a regional anaesthetic technique in cases classified as urgent did not influence the incidence of admission to the special care baby unit[5]. The authors concluded that while general anaesthesia was indicated for cord prolapse, severe sustained bradycardia and significant antepartum haemorrhage, its use for cardiotocograph diagnosed fetal distress can generally be avoided.

General anaesthesia carries considerable risk for mother and baby. Obstetric anaesthetists need to be aware that its use for Caesarean section for fetal distress is often not justified.

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1. Hawthorne L, Wilson R, Lyons G, Dresner M. Failed intubation revisited: 17-yr experience in a teaching maternity unit. *British Journal of Anaesthesia* 1996; 76: 680–684.
2. Chadwick HS, Posner K, Caplan R, Ward RJ, Cheney FW. A comparison of obstetric and non-obstetric malpractice claims. *Anesthesiology* 1991; 74: 242–249.
3. *Report on Confidential Enquiry into Maternal Deaths in Great Britain in 1984–1987.* London: HMSO, 1991.
4. Ng PC, Wong MY, Nelson EA. Paediatrician attendance at Caesarean section. *European Journal of Pediatrics* 1995; 154: 672–675.
5. Quinn AJ, Kilpatrick A. Emergency caesarean section during labour: response times and type of anaesthesia. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1994; 54: 25–29.

Sir,—Dr Norman's letter concerns itself with the choice of anaesthetic technique for the compromised fetus and our audit dealt specifically with intubation during general anaesthesia. Our series of failed intubations spanned 17 yr, during which time techniques and attitudes have changed. Dr Norman touches on one point in a series of complex arguments, all of which are outside the remit of our audit. While we appreciate his interest and comments on our article, it would be inappropriate to comment further.

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Sir,—I read with interest the review of the management of failed intubation in obstetric anaesthesia by Hawthorne and colleagues[1]. In their series of 23 failed intubations, manual ventilation of the lungs was difficult or impossible in 39% of patients while the airway was maintained before patients regained spontaneous ventilation. Despite this, the authors advocate in their failed intubation drill that all patients should be managed in the left lateral, head-down position during this critical period.

In my opinion there is no evidence to suggest that the traditional teaching of adopting the lateral position in such circumstances is better than leaving the patient in the supine position with left lateral tilt. Turning these patients who are often obese into the lateral position exposes them to a greater risk of failed ventilation and ineffective cricoid pressure. Unfamiliarity with the lateral position is compounded by the need for two-handed techniques both to maintain an adequate seal between face mask and patient and adequate cricoid pressure. A third pair of often unskilled hands then becomes necessary to squeeze the reservoir bag to provide ventilation. The reduced risks of aspiration of gastric contents because of preferential gravitational spill from the mouth of any regurgitated material instead of into the trachea is of little benefit if the risks of hypoxia and regurgitation are increased by such a manoeuvre. I believe the anaesthetist's and anaesthetic assistant's abilities to maintain an airway and prevent regurgitation are optimized by leaving these patients supine when a failed intubation drill is implemented. A trial of release of cricoid pressure may still necessitate a head-down tilt. In addition, the authors suggested reducing cricoid pressure earlier in their regimen to improve a grade 4 view at laryngoscopy with the patient still supine, and no advantage is gained by turning the patients at a later stage to repeat the manoeuvre.

The second reason for leaving these patients supine is that the last recourse for managing the "failure to intubate, failure to ventilate" scenario is to perform a cricothyroidotomy, which I note was attempted in one case. The authors did not state if this was performed with the patient on their side, but I would suggest this is very difficult if not impossible to do in such circumstances.

Finally, I would suggest that spinal anaesthesia is the only method of regional anaesthesia suitable in the subsequent management of such patients for Caesarean section. If an extradural or a combined spinal–extradural technique is used, as occurred in 43% and 13% of patients, respectively, in the reported series, there remains a risk of intrathecal or intravascular injection of a large quantity of local anaesthetic via the extradural catheter, despite an initial negative test dose. Failure to intubate the trachea if then required in such circumstances would no doubt be catastrophic and could be avoided by the use of a spinal anaesthetic technique.

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1. Hawthorne LA, Wilson RC, Lyon G, Dresner M. Failed intubation revisited: 17-yr experience in a teaching maternity unit. *British Journal of Anaesthesia* 1996; 76: 680–684.

Sir,—McBrien makes two points in his letter. First, rather than turning the patient to the left lateral, head-down position, it may be advantageous to leave the patient supine, and second, because extradural anaesthesia has a risk of intrathecal or i.v. injection, spinal anaesthesia should be recommended. He does not provide evidence in support of his ideas.

The debate as to the best position in which to conduct the failed intubation drill is longstanding. On the one hand is the Tunstall view[1], and on the other is that of Rosen[2]. Rosen did not appear to provide any data in support of his view, but in our series of 17 cases there were no instances of regurgitation or aspiration. It is only at the point where general anaesthesia is abandoned that the patient is turned. In fact, turning to the left lateral position may facilitate a view of the vocal cords. When surgery is to continue and general anaesthesia is maintained, the patient remains in the semi-prone, head-down position.

Inadvertent intrathecal or i.v. injection with extradural anaesthesia is a remote, but real risk, as is high spinal anaesthesia. In our series we had no problems with any regional technique, and the relative risks of one against the other are unknown.

Much of the data concerning the problems with intubation in obstetric practice represent no more than the opinions of the authors. We have sought publication of the only audited performance of a failed intubation drill to provide the sub-specialty with some support for clinical practice.

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1. Tunstall ME. Failed intubation drill. *Anaesthesia* 1976; 31: 850.
2. Rosen M. Difficult and failed intubation in obstetrics. In: Latto IP, Rosen M, eds. *Difficulties in Tracheal Intubation.* London: Baillière Tindall, 1985.

Sir,—Hawthorne and colleagues' recent review of failed obstetric intubations in their maternity unit[1] stated that despite a decrease in obstetric general anaesthetics they have seen an increase in failed intubation from 1:300 in 1984 to 1:250 in 1994. Against a background of approximately 300 obstetric general anaesthetics per year and an incidence of failed intubation of approximately 1 per year, it is not possible to say that this change represents a real increase. Furthermore, the fact that they have seen an increase in the total number of Caesarean sections performed implies that a decrease in the use of general anaesthesia from 83% in 1981 to 23% in 1994 represented only an approximate 30% reduction in the total number of general anaesthetic Caesarean sections. Consequently, it is not surprising that they had the impression that they had not seen a reduction in the incidence of failed intubation. Fortunately, failed intubation is a rare occurrence. This implies that the effectiveness or otherwise of a difficult intubation drill is necessarily difficult to demonstrate.

In addition, the difficult intubation flow diagram described seems to suggest that in cases of fetal distress and maternal haemorrhage where direct laryngoscopy is grade 3 (Cormack and Lehane), failure to intubate should be followed by the use of the laryngeal mask but in grade 4 laryngoscopy one should institute the failed intubation drill. Precluding the use of a laryngeal mask airway in this type of emergency based on whether or not the tip of the epiglottis can be seen on direct laryngoscopy does not seem justified. Moreover, grade 2 laryngoscopy may be associated with difficult intubation, particularly in obstetric patients.

It is interesting that in the six patients who underwent indirect laryngoscopy after operation no abnormality was found. In a study nearing completion, we have found a highly significant association between difficult indirect laryngoscopy and difficult intubation. The only failed obstetric intubation that was included in our study was an easy indirect laryngoscopy. These findings support the suggestion that failure to intubate the trachea of obstetric patients is more often a result of changes caused by pregnancy and the particular problems of attempting to intubate in less that ideal circumstances than because of the anatomical features that make the intubation of non-pregnant patients difficult.

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1. Hawthorne L, Wilson R, Lyons G, Dresner M. Failed intubation revisited: 17-yr experience in a teaching maternity unit. *British Journal of Anaesthesia* 1996; 76: 680–684.

Sir,—We thank Dr Kessell for the interest shown in our review of failed obstetric intubation in which he makes the following points. On the basis of the relative incidence of obstetric general anaesthetics and failed intubations, we would be unlikely to identify any changes, and the effectiveness of a failed intubation drill would be difficult to demonstrate. He also comments on the place of the laryngeal mask and supports our impression that the anatomical features are not the main culprit in failure to intubate in the obstetric setting.

The figures that Dr Kessell quoted are our own, and we do not wish to conceal our disappointment at our failure to reduce the incidence of failed intubation. We acknowledge that it is difficult to confirm the effectiveness of a failed intubation drill, and we wish to point out that ours is the only documented audit of its application in obstetric practice. We have not attempted to undertake a statistical analysis of this data as it would be inappropriate; none the less, we feel that our results are clinically relevant.

Dr Kessell may be correct about placement of the laryngeal mask airway (LMA). Since the publication of our article, we have become aware of a report of the use of the LMA in 224 women undergoing Caesarean section, including 49 emergencies, apparently without any significant problems and a success rate of 99%[1]. As more information supporting the safe use of the laryngeal mask becomes available, we anticipate that it may become the first alternative when tracheal intubation fails.

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1. Liew E, Chan-Liao M. Experience of using laryngeal mask anaesthesia for Caesarean section. *11th World Congress of Anaesthesiologists,* 1996; D771.

Perioperative mucosal pH_i in orthotopic liver transplantation

Sir,—We read with much interest the recent article by Welte and colleagues[1]. In their study, the authors found a significant decrease in intramucosal gastric pH (pH_i) during the anhepatic stage of liver transplantation, even though venovenous bypass (VVB) was used. These values became normal during the reperfusion stage of the graft. In our experience[2], with or without the use of VVB, pH_i was normal in the former group but a significant decrease was observed in the group without VVB (table 1).

As in Welte's study, pH_i values became normal after reperfusion of the graft. However, in contrast with these authors, our patients showed a higher baseline pH_i, which could explain the differences observed during the anhepatic stage in the VVB patients. Maintaining temperature in our patients and improved global oxygenation because of vena caval preservation during the anhepatic stage may account for these differences.

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1. Welte M, Pichler J, Groh M, Jauch KW, Pratschke FP, Haller M, Frey L, Peter K. Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation. *British Journal of Anaesthesia* 1996; 76: 90–98.
2. Camprubi I, Sabate A, Mainer A, Dalmau A, Torras J, Figueras J, Jaurrieta A. Percutaneous venovenous bypass

Table 1 Effects of percutaneous venovenous bypass (VVB) on intramucosal gastric pH (pH_i), cardiac index (CI), temperature and oxygenation in group GA (VVB used; n=10) and group GC (no VVB used; n=10) during hepatectomy (TI), the anhepatic stage (T2) and after reperfusion (mean (SD)). *P<0.05 between groups

	T1 GA	T1 GC	T2 GA	T2 GC	T3 GA	T3 GC
CI (litre m^{-2} min^{-1})	5.4 (1.2)	5.3 (2.1)	4.5 (1.5)	5.9 (2)	5.9 (1)	5.8 (1.4)
Oxygen extraction (%)	17 (1.5)	13 (2)*	14 (3)	14 (6)	23 (5)	20 (3)
Temp. (°C)	35.5 (0.6)	35.7 (0.7)	34.8 (0.7)	35.3 (0.3)	34.9 (1)	35.7 (0.7)*
Lactate (mmol $litre^{-1}$)	2.3 (1)	2.6 (1.3)	4.5 (1)	4.7 (1.7)	4.7 (2)	5.3 (1)
pH_i	7.392 (0.1)	7.400 (0.1)	7.408 (0.1)	7.253 (0.1)*	7.357 (0.1)	7.389 (0.1)

(VVB) in liver transplantation (LT): A randomized study. Preliminary results. *Liver Transplantation and Surgery* 1995; 1: 415 (abstract).

Sir,—We appreciate the letter of Camprubi and Sabate which relates to our recent article on mucosal pH (pH$_i$) during orthotopic liver transplantation (OLT)[1]. Their preliminary data suggest that the use of venovenous bypass (VVB) during the anhepatic stage of OLT may indeed be beneficial for mucosal oxygenation: in contrast with our results, gastric pH$_i$ was preserved with VVB, but decreased transiently without VVB. As pointed out in our article, we were unable to strictly test the hypothesis that VVB would maintain mucosal blood flow as VVB was used routinely at our institution. Therefore, we cannot exclude the possibility that pH$_i$ values might have decreased to even lower values without VVB. The main purpose of our study was to assess the ability of tonometry to detect intraoperative mucosal hypoxia, to measure gastric and sigmoid pH$_i$, and to relate the observed changes in pH$_i$ to the occurrence of endotoxaemia and primary graft function.

Although in the preliminary report of Camprubi and colleagues, important information on patient physical status and determinants of tissue oxygenation is lacking, the fact that cardiac index, oxygen extraction and lactate concentration are comparable with the values measured in our study suggests that the different results for gastric pH$_i$ during the anhepatic stage may be attributed to the more severe chronic impairment of intestinal perfusion in our patients with end-stage cirrhosis. This is supported by the lower pH$_i$ values measured early during hepatectomy in our study (7.28 *vs* 7.39). In fact, low pH$_i$ values (<7.32) have been reported in patients with chronic intestinal ischaemia and portal vein obstruction[2]. In agreement with our data, the pH$_i$ values of Camprubi and colleagues' patients without VVB had returned to baseline after reperfusion. However, in our patients with end-stage hepatic cirrhosis, pH$_i$ did not reach normal values (>7.32) before the second postoperative day, an observation that further supports the presence of chronic impairment of mucosal microcirculatory perfusion. Hence, pre-existing chronic mucosal hypoxia might explain why pH$_i$ decreased during the anhepatic stage, although overall portal flow was maintained by the use of VVB.

It also cannot be excluded that the apparent difference in baseline pH$_i$ values between our study and that of Camprubi and colleagues is a result of the use of different blood-gas analysers. Riddington and colleagues[3] and Takala and colleagues[4] have shown that direct comparison of pH$_i$ values obtained by different analysers is not valid. Therefore, it was recommended that each institution should determine its own reference values for pH$_i$.

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1. Welte M, Pichler B, Groh J, Anthuber M, Jauch K-W, Pratschke E, Lenhart FP, Haller M, Frey L, Peter K. Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation. *British Journal of Anaesthesia* 1996; 76: 90–98.
2. Fiddian-Green RG, Stanley JC, Nostrant T, Phillips D. Chronic gastric ischemia—A cause of abdominal pain or bleeding identified from the presence of gastric mucosal acidosis. *Journal of Cardiovascular Surgery* 1989; 30: 852–859.
3. Riddington D, Venkatesch KB, Clutton-Brock T, Bion J. Measuring carbon dioxide tension in saline and alternative solutions: quantification of bias and precision in two blood gas analyzers. *Critical Care Medicine* 1994; 22: 96–100.
4. Takala J, Parviainen I, Siloaho M, Ruokonen E, Hämäläinen E. Saline PCO_2 is an important source of error in the assessment of gastric intramucosal pH. *Critical Care Medicine* 1994; 22: 1877–1879.

Volatile anaesthetics and neuromuscular block

Sir,—I read with interest the article by Dr Vanlinthout and co-workers[1] and agree that the magnitude of potentiation of the effects of neuromuscular blocking agents by volatile anaesthesia is an important clinical question. We established recently that the dose of vecuronium required for a given effect during desflurane anaesthesia was 20% less than that required during isoflurane anaesthesia[2]. Consequent from this small reduction in vecuronium dose requirements there was a much greater degree of recovery from the neuromuscular blocking agent when the concentration of desflurane was reduced compared with equivalent reductions in isoflurane. Hence, even small differences in potentiation can be of great clinical significance if neuromuscular blockers are administered in response to monitoring (thereby taking advantage of reductions in dose requirements).

Dr Vanlinhout's group set out to clarify inconsistencies in the literature on the interaction between sevoflurane and neuromuscular blocking agents. Unfortunately their study merely adds to the confusion. They concluded that sevoflurane and isoflurane potentiated neuromuscular blocking drugs to a similar degree. It is not reasonable to draw such a conclusion from the data presented in their article.

For vecuronium alone, they found an ED_{50} value of 16.9 μg kg^{-1}. With the degree of variability reported and assuming that a 20% reduction in dose requirements is clinically relevant[2], their study had, at best, only an 11% chance of demonstrating such a reduction. That is, if the reduction in vecuronium dose reported in the presence of sevoflurane (ED_{50} of 14.4 μg kg^{-1}, 17% less than with isoflurane) was a real (rather than chance) occurrence, then 204 patients would have to have received each anaesthetic to have an 80% chance of demonstrating such a difference at the 0.05 significance level.

We should interpret their study with caution. The results of their study are entirely in keeping with there being a clinically important difference in the degree of neuromuscular blocker potentiation manifest by sevoflurane and isoflurane.

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1. Vanlinthout LE, Booij LD, Van Egmond J, Robertson EN. Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium, and atracurium. *British Journal of Anaesthesia* 1996; 76: 389–395.
2. Wright PM, Hart P, Lau M, Brown R, Sharma ML, Gruenke L, Fisher DM. The magnitude and time course of vecuronium potentiation by desflurane versus isoflurane. *Anesthesiology* 1995; 82: 404–411.

Sir,—Clinical interaction studies evaluating the influence of different anaesthetic techniques on the action of neuromuscular blocking agents often compare two or more groups of patients treated separately but concurrently as part of the same study. These studies are termed "parallel" to emphasize their difference from other clinical studies in which patients are their own controls. Parallel comparisons include most of the usual forms of interaction studies investigating the abilities of different inhalation anaesthetics to potentiate the neuromuscular effects of neuromuscular blocking agents. However, the large between-patient variability in dose–response and dose–duration studies with neuromuscular blocking agents may preclude demonstration of subtle differences in susceptibility to these agents. Paired crossover studies can minimize the effect of inter-individual variability[1]. However, these paired crossover studies are difficult to perform with surgical patients. Healthy ASA I or II patients that are anaesthetized two or more times, receiving on each occasion a different anaesthetic technique, are rare. Therefore, these paired crossover studies have to be performed with volunteers.

Our clinical study was designed as a parallel comparison of different anaesthetic techniques, that is opioid–nitrous oxide–oxygen, opioid–nitrous oxide–oxygen–isoflurane and opioid–nitrous oxide–oxygen–sevoflurane, in their ability to potentiate the neuromuscular effects of the most commonly used non-depolarizing neuromuscular blocking agents in surgical patients. Using one-way analysis of variance (ANOVA) and subsequently the Ryan–Einot–Gabriel–Welsh (REGW) multiple range test[2] to identify eventual sources of difference, there was a significant difference in magnitude and duration of neuromuscular action between the control group, receiving no volatile agent, and the groups receiving inhalation anaesthetics. We were unable to demonstrate any significant difference between opioid–nitrous oxide–oxygen–isoflurane and opioid–nitrous oxide–oxygen–sevoflurane anaesthesia on the effects of neuromuscular blocking agents. In the population investigated, the differences between opioid–nitrous oxide–oxygen–isoflurane and opioid–nitrous oxide–oxygen–sevoflurane anaesthesia on the magnitude and duration of neuromuscular blocking agents were small compared with the between-patient differences in these responses to neuromuscular blocking agents ($<10\%$ for the mean values of both magnitude and duration of action). In order to demonstrate significant differences in the potentiating abilities of isoflurane and sevoflurane on the effects of neuromuscular blocking agents, that is a significant difference in both depth and duration, sample sizes of several hundreds of patients per neuromuscular blocking group would have been required[3]. Such sample sizes are beyond practicable limits. We selected our population carefully, using rigid inclusion criteria, as described in the text, to reduce patient variability. This inevitably introduced constraints such as the availability of large numbers of eligible patients within a reasonable period of time. Any investigator is limited by both resources and time. Additionally, our study was intended as a phase II trial to evaluate the interaction between sevoflurane and neuromuscular blocking agents within a limited number of surgical patients.

Both the investigator and clinician should be concerned about the ability to detect an important clinical difference. Different investigators disagree on what is a clinically significant difference. They also disagree on the risk they are willing to take of missing a meaningful effect caused by drug interaction[4]. The choice of a 20% difference in ED_{50} as a clinically significant value is arbitrary. Such a difference is small compared with the large inter-individual differences in the response to neuromuscular blocking agents. With the degree of variability and sample sizes used in our study, a 30% reduction in the ED_{50} of pancuronium and atracurium and a 45% reduction in the ED_{50} of vecuronium had an 80% chance of being significant at the 0.05 level.

Finally, we still feel that further interaction studies on the influence of higher concentrations of volatile anaesthetics on larger doses of neuromuscular blocking agents are warranted. To elucidate small but significant differences in the ability of isoflurane and sevoflurane to potentiate the action of neuromuscular blocking agents, these interaction studies need to be performed in volunteers who are studied twice, receiving isoflurane on one occasion and sevoflurane on the other[5].

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1. Lavori PW, Louis TA, Bailar JC III, Polanski M. Designs for experiments—parallel comparisons of treatment. *New England Journal of Medicine* 1983; **309**: 1291–1299.
2. Begun JM, Gabriel KR. Closure of the Newman–Keuls multiple comparison procedure. *Journal of the American Statistical Association* 1981; 76: 374–375.
3. Snedecor GW, Cochran WG. *Statistical Methods*, 8th Edn. Ames, Iowa: Iowa State University Press, 1989; 83–106.
4. Fredman JA, Chalmers TC, Smith H, Kuebler RR.The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *New England Journal of Medicine* 1978; **299**: 690–694.
5. Wright PMC, Hart P, Lau M, Brown R, Sharma ML, Gruenke L, Fisher DM. The magnitude and time course of vecuronium potentiation by desflurane versus isoflurane. *Anesthesiology* 1995; **82**: 404–411.

Cusum: a statistical method to evaluate competence in practical procedures

Sir,—It was interesting to read the commentary by Kestin[1] describing the use of cusum analysis to measure the competence of anaesthetic trainees at practical procedures. The cusum is a useful graphical tool for discerning trends from a series of observations. The derivation of boundary lines for sequential tests allows comparison of the observed proportions of success or failure against predetermined standard criteria. This could be developed into a continuous performance monitor in anaesthesia.

In his article, Kestin discussed the problems of keeping paper records and plotting fractions on the graphs. In response to this we set out to develop a computerized personal log book system for practical procedures to run in parallel with the electronic anaesthetic log book on the Psion 3a. However, in setting up the algorithms we have encountered a number of problems.

The values for s, h_0 and h_1 calculated using the formulae in the appendix do not agree with the values in table 1 of the article. On reviewing the original articles[2] on the application of the cusum, the value of Q should read $Q = \text{Ln}\ [(1-p_0)/(1-p_1)]$. The values in the table are indeed correct if this calculation is used for Q.

The null hypothesis in the article is stated as "the true failure rate is NOT different from the acceptable failure rate" and if the cusum exceeds h_1 then it is rejected. This does not imply that the true failure rate exceeds the unacceptable failure rate which is the performance indicator which interests us. Similarly the alternative hypothesis is stated as "the true failure rate is equal to or exceeds the unacceptable failure rate" and if the cusum decreases to less than h_0 then it is accepted. Surely this would imply that the falling cusum of registrar B in figure 1 has a true failure rate that is equal to or exceeds the unacceptable failure rate.

p_0 corresponds to the failure rate under the null hypothesis which should surely read "the true failure rate is not different from the unacceptable failure rate". If the cusum exceeds h_1 then this hypothesis is accepted and the trainee's performance is unacceptable with reference to the agreed unacceptable failure rate. Similarly p_1 corresponds to the failure rate under the alternative hypothesis which should surely read "the true failure rate is equal to or exceeds the acceptable failure rate". If the cusum decreases to less than h_0 then the this hypothesis is rejected and the trainee's performance is no worse than the accepted failure rate.

Furthermore, there appear to be clearcut criteria in the definition of success or failure for a particular procedure. This is confusing and it is difficult to see why type 1 and 2 errors of 10% (0.1) where chosen.

For reasons of convenience for the plotting of the graph, the values of s, h_0 and h_1 where multiplied by 10. It is not clear if, in the event of a success, $(1-s)$, $10\ (1-s)$ or $1-10s$ was plotted.

The statistical method described by Kestin appears to be a very powerful analytical tool and may have a wide range of applications in the assessment of trainees. However, the errors and inconsistencies in the appendix are a source of confusion. It would be useful if the derivation of the definitions, variables, hypotheses and theory behind the calculations were explained more clearly.

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1. Kestin IG. A statistical approach to measuring the competence of anaesthetic trainees at practical procedures. *British Journal of Anaesthesia* 1995; **75**: 805–809.
2. Williams SM, Parry BR, Schlup MMT. Quality control: an application of the cusum. *British Medical Journal* 1992; **304**: 1359–1360.

Sir,—I would like to thank Drs Hammond and McIndoe for their interest, and in particular for correcting the error in the formula for Q in the appendix—p_0 and p_1 have been transposed.

In answer to their other comments, the advantages of using α and β of equal magnitude is explained in the methods section; the choice of 0.1 was a compromise between the common values for α of 0.05 and for β of 0.1 or 0.2 used in clinical studies. The software on the Psion 3a can be used to record and display the cusum; in this case, it is not as helpful to have α and β equal than if graphical methods are used. The graphs used by our trainees were plotted using the nearest integers to $10s$ and $10\ (1-s)$ as the increments.

The original article in the *British Medical Journal* referred to by Drs Hammond and McIndoe was the article that stimulated my interest in this topic. However, I found it difficult to understand the basic statistical concepts of cusum analysis from this article. I found it even more difficult to write an explanation myself, and this article is the only one of mine which the reviewers have ever suggested that more text be included to clarify the argument! I would refer them and others to Davies' text[1] for a better explanation than I could provide.

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1. Davies OL. *The Design and Analysis of Industrial Experiments*, 2nd Edn. London: Longman Group, 1978.

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BOOK REVIEWS

Critical Care: Standards, Audit and Ethics. J. Tinker, D. R. G. Browne and W. J. Sibbald (editors). Published by Arnold, London. Pp. 412; indexed; illustrated. Price £85.00.

This book is divided into four sections: critical care, resource standards, audit and ethics. The editors take the view that technology is no longer the limiting factor in the management of the critically ill patient and have therefore gathered together expert views on these other issues which challenge intensive care clinicians. The authorship is chosen to give a global perspective, and the variety of content to provide something for everyone (intensive care clinicians, students, trainees, lawyers and hospital managers). Indeed, it is difficult to avoid the opinion that many sections are written for lay persons.

The introductory sections suggest that critical care medicine is life-support biology and the unit where it is practised, the hospitals' hospital. Clear differences emerge between nations and their provision of intensive care and individuals involved in its delivery. "The clinical pharmacist has participated in the full care of the patient with special effectiveness during life-threatening crises, including those of cardiac arrest." Repetition of iatrogenic complications introduced by intensive care medicine is a good reminder of our responsibilities. On the whole, the text is well referenced, with the occasional exception (a reference to fatal consequences of tracheostomy, almost certainly performed surgically, from 35 yr ago). The book covers development and cost implications of intensive care medicine and implications for the future.

The second large section on resource standards is an odd mixture of chapters and topics covering primary care and transport, general structure of intensive care units, monitoring and a shopping list of the therapies that are provided. There are some good sections on the use of unevaluated invasive monitoring, excuses for compassionate use of unproved therapy, and the difficulties in defining risk benefit. The theme throughout is the lack of evidence for benefit of intensive care but the justification for failure of mortality to improve is that we are now treating older, sicker patients in whom more general medical effort has been put into sustaining those with chronic disease. "The logical progression of ethical arguments can be developed by which specific therapies or diagnostic procedures are defended."

The chapter on invasive haemodynamic monitoring suggests we should apply specific tests for documentation of the effectiveness of this monitoring and provides an excellent section on the fantasies of haemodynamic monitoring, particularly related to the limitations of measurement of pulmonary artery occlusion pressure. The need for future research studies, especially on the use of pulmonary artery catheterization to rationalize cost containment, is clearly evident. The chapter on imaging describes the basic techniques available and the radiological appearance of pathological processes in different anatomical sites. This would benefit from more illustrations of better quality. The section on the intensive care laboratory is particularly good as few of us have looked in adequate depth at our procedures for quality assurance and quality control. These authors have achieved their objective of presenting a philosophy to eliminate errors and the requirement for documentary evidence of QC, service records and staff training.

I had some anxiety that the views of the authors represented in the chapters on delivering respiratory, cardiac and renal support, although conventional, would be viewed as the standard approach for all patients, given the nature of the text.

There are very useful comparisons of nursing and medical staffing and training, including those for respiratory and physical therapy, between the UK, USA, Australia and Canada and an innovative chapter on the role of the clinical engineer and clinical scientist in patient care. This latter section bewails the lack of worldwide recognition for academic qualifications, certification or registration which the author suggests adversely affects the professional profile and status of clinical scientists, engineers and technologists at a time when complex technological management requires a highly qualified person with managerial skills who must also be proficient in computing and budgeting, in addition to being involved in clinical trials.

The section on audit which adapts the general principles to intensive care is well written and draws attention to the potential for patient data management systems to integrate information. There is some repetition in the later part of the book in relation to selection of patients for intensive care which is inevitable as it alludes to the means of quantifying illness. The limitation of outcome measurements is referred to and also the potential for "negative benefits". The overall outcome from intensive care has to be viewed however as part of the integrated process of health care delivery. The authors of the chapter on costs and consequences evaluating the evidence of benefit of intensive care has achieved its objective in providing insight into technology assessment and making clear recommendations that we improve our ability to critically evaluate the technologies we use, a challenge which is being met in the UK by Health Technology Assessment bodies and better liaison with industry to work towards developments which will help patients and not sales.

The section on ethics defines our need to establish priorities in order to make choices within health care and draws attention to the high incidence of withdrawing or withholding care as a prelude to death in the ICU. There are considerable international differences in practice and good if simplistic advice from the European author to resist fears of malpractice suits when facing futile prolongation of life.

The section on organ donation is very comprehensive although the use of xenografts is dismissed by a few lines without any reference to the potential for the spread of blood-borne viral disease in the immunocompromised host. The requirement to achieve good standards in clinical research is stressed and this chapter covers the ethical issues and the requirement of researchers to be not only good physicians but capable of conducting a study that will help to improve patient care in the future.

Inevitably, the medico–legal section contains a good deal of repetition, again from other sections of the book, but provides good insight into international differences in approach and indeed variations in pronouncements from our own legal system in the UK, particularly relating to withdrawal of care where the decisions of judges inevitably reflect their own moral stance. The book ends with a chapter on moral and religious dilemmas, with particular reference to management of the Jehovah's Witness.

Overall, I would recommend this book to all those involved in the delivery of intensive care. It does try to deliver all things to all people, but perhaps because of this we are encouraged in our multidisciplinary attitude to consider these important issues not only for ourselves but in the context of the rest of the developed world.

S. Willatts

Comprehensive Human Physiology from Cellular Mechanisms to Integration, vols 1 and 2. G. Greger and U. Windhorst (editors). Published by Springer, Berlin. Pp. 2527; indexed; illustrated. Price DM168.00.

The first thing that struck me about these volumes was their massive size—postage for the two volumes was just under £10. Together they contain about four times the content of a "standard" physiology text, such as Ganong, and each volume is equal to one of the larger textbooks, such as Best and Taylor. Thus, in content, it comes between the usual textbook range and the highly voluminous, highly expensive encyclopaedic work such as the *American Physiological Society Handbook of Physiology*. The hard cover binding is excellent in that the volumes remain open at any selected page on a flat surface. The paper and print quality are also excellent, although the print size is smaller than in most textbooks.

The editors state two main aims: first, to provide an up-to-date review of the subject of human physiology, and second, to combine molecular and cellular information with integrated whole-body physiology. To achieve this they have enlisted some 104 contributors, mainly from Germany (47) and North America (30 from the USA and nine from Canada); only four are from the UK. The 124 chapters (and two appendices) are organized into five major sections: basic principles and their coordination (476 pages); the nervous system (720 pages) (end of volume one); intake and excretion (434 pages); acute vital functions, heart, circulation and respiration (580 pages); and the life cycle (190 pages). There is an initial chapter on "Physiology past and future", the last chapters are on the physiology of aging and death and there are generous appendices (29 pages) on physiological units and normal values for physiological variables. The index covers 77 pages and is present only in volume two, whereas the preface, list of contents and contributors are given at the front of both volumes. As a sign of the times, the final page of each volume is entitled "Springer-Verlag and the environment", and states that the materials used, including paper from low- or no-chlorine pulp, are environmentally friendly.

The book is liberally illustrated (black/blue with occasional full colour) with high quality diagrams and original micrographs, traces and data. Most chapters end with 100 or more primary references. Overall the style is clear and elegant. Much of the book is written in a user friendly style but some readers may find some areas difficult to digest. Chapters often end with a conclusions section which may be a brief summary paragraph or extend to a full page.

I feel that the editors have achieved their aim of providing a state-of-the art comprehensive review of human physiology from the molecular to the whole organism level. The chapters, written by subject experts, are scholarly in style, with discussion of evidence and citation of numbered references at the end of each chapter. Content approximates to monograph level. The references cover the late 1980s and the 1990s. Thus in one highly referenced chapter, 35 of the 233 references are from the 1990s, including two in press, and 103 are from the 1980s. I feel that most would be gained from this book by reading complete chapters, some of which are heavy going in places, rather than using the book to check a point of basic detail in a short space of time, where established textbooks would probably be better.

From being personally involved in a (rather smaller) multi-author publication, I can appreciate the enormous effort required to get this huge enterprise off the ground. The preface records that, sadly, the two original editors (Mommaerts and Koepchen) both died before the work could be brought to fruition. The publisher's current advertisement gives the pages as approximately 1860, and from my own experience I would see the first edition as essentially a starting point and hope that the momentum can be maintained by further editions at relatively short intervals, now that modern word-processing makes updating and improving relatively painless.

In conclusion, this is certainly not a book for the trainee anaesthetist working for the fellowship. Even the intellectual high flyer would be better advised to use one of the excellent larger textbooks. However, at a cost of DM 168 (about £73) it represents excellent value and I would strongly recommend it for departmental and hospital libraries and for individuals looking for "in-depth" updates across the range of physiological knowledge. If the editors and authors can refine and update it every 2 or 3 yr then I think it could become a classic and perhaps confound the editors' prediction in the last paragraph of their preface that we are "on the verge of an era without printed textbooks".

W.F.M. Wallace

Critical Care of Infants and Children. I. D. TODRES AND J.-H. FUGATE (editors). Published by Little, Brown and Co., Boston. Pp. 725; indexed; illustrated. Price £85.00.

This single volume, competitively priced, American text joins an expanding list of books in the fledgling 38-yr-old specialty of paediatric intensive care which is still "*in utero*" in the UK, at least in terms of its provision, organization and training. The contents are prioritized well, with resuscitation, emergency management and practical procedures covered in the first 100 pages, with useful line drawings, photographs and radiographs sprinkled liberally throughout the text. I was surprised that there was no paediatric CPR algorithm in the first chapter and in the section on upper airway obstruction, the general anaesthesia technique used for securing the airway was given the body swerve, presumably because American intensivists do likewise by delegating this duty to the anaesthetist!

The "systems" are covered well and an interesting chapter on cardiac ultrasound is illustrated well with Doppler photographs, including five colour plates. Nitric oxide and high frequency oscillation are mentioned briefly and deserved more coverage, and liquid ventilation, which has great potential, was omitted. Pharmacology and poisoning are reviewed but it was interesting that the references on "propofol poisoning", which caused such problems in the UK, were not mentioned. The last part of the book attempts to deal with the extremely important ethical, psychosocial and organizational issues which impact more and more on paediatric intensive care practice. The key role of the intensivist as a coordinator is stressed and the dangers inherent in too much "multidisciplinarianism" illustrated nicely by the poem *The blind men and the elephant* by J. G. Saxe, which gives welcome light relief.

The last paragraph in the book sums up why some of us struggle on with our love–hate relationship with paediatric intensive care: "The importance of a well organised and smoothly run ICU is critical to the care of the child and the family. For the intensivist, the experience can be a most rewarding one, providing a great source of satisfaction and the opportunity to be a true healer".

N. S. Morton

Anaesthesia Review 12. L. KAUFMAN AND R. GINSBURG (editors). Published by Churchill Livingstone, Edinburgh. Pp. 259; indexed; illustrated. Price £35.00.

Wisely seeing no need to alter their tried and tested format, the (now joint) editors of *Anaesthesia Review* present the 12th volume in this popular series. Twelve chapters by invited contributors provide informative, up-to-date, relevant and mostly readable reviews of a diverse array of topics, with a bias in this volume towards pharmacological developments and aspects of pain relief. Dr Kaufman provides two rather less easy-to-read chapters packed with interesting tit-bits of information relating to recent publications in anaesthesia, and in medicine relevant to anaesthesia. These serve as a valuable reference source to further their knowledge in a particular field. Perhaps the inclusion of a research paper in a Dr Kaufman review chapter could be used as a marker of relevance to the average anaesthetist!

The 12 invited contributions, mostly by known authorities in their field, vary in style, length and depth; the authors appear to have had a fairly free hand in this matter. This is by no means a criticism, as it enables the reader to select his/her reading to suit the time and concentration faculties available. Topics range from alternative methods of ventilation in ARDS to end-tidal carbon dioxide monitoring, the spinal cord and chronic pain, controversies in pain, transdermal drug delivery, infusion techniques, paediatric analgesia, oxidant injury, metabolism of newer anaesthetic drugs, extradural anaesthesia, anaesthesia for burns patients and prevention of venous thrombosis. Every chapter is well-referenced and there is little to criticize. I found no factual errors and only a few spelling or typographical errors.

It is customary to recommend a book such as this to FRCA candidates. I would suggest that while examination candidates would undoubtedly benefit from selective reading of this book, there are probably more time- and cost-efficient methods of learning. It would be useful reading to have in the on-call room or on the train, or for regaining momentum in that post-written, pre-viva announcement period. For the rest of us with rather less pressure and a little more time, this book is an enjoyable read over a few weeks, with much of interest to most anaesthetists.

D. Campbell

Clinical Risk Management. C. VINCENT (editor). Published by BMJ Publishing Group, London. Pp. 570; indexed. Price £34.95.

This is a 500 page paperback book produced by the BMJ Publishing Group; each chapter is written by a different author and edited by the psychologist, Charles Vincent.

Resource management is a developing subject in health care in this country, which is fuelled by increasing clinical negligence cases for which trusts have to take responsibility, the realization of the frequency of mistakes in health care practice and that "human rather than technical failures now represent the greatest threat to complex and potentially hazardous systems".

This book gives a thorough and comprehensive review of the state of this subject in the UK at the present time and a rational opinion of both how it should, and how it is likely to develop. It does this by collecting together a series of essays by different authors which are mostly very readable and have some common thread of style. It is divided into three parts. The first part gives the background to the subject with a chapter on experiences from the United States and chapters on the psychology of human error and changing behaviour. The chapter on financial implications of risk management points out that if resource management is seen only in terms of litigation and finance, it is difficult to prove its worth, but in terms of quality improvement, there are both social and economic benefits to be gained from reducing untoward outcomes. The close link between risk management and quality improvement is discussed, but it is emphasized that they appear to be aimed at different groups and have different financing arrangements although they should be part of the same system. Also, the close link between clinical and management activities is firmly established.

In the second part of the book, risk management is dealt with in a more practical way, with chapters on the state of risk management in a number of specialties, including obstetrics, A&E and anaesthesia, and chapters on general practice and risk management in nursing and midwifery. Several of these chapters are well illustrated by case studies and other examples which make interesting reading to the practising clinician. They show the diverse interpretation of risk management in different specialties which, although partly a result of the different needs of the different specialties, also illustrates the need for considerable improvement in many areas.

The third part deals with the practical aspects of how to implement a risk management programme. Although some of the views in this part are expressed from a fairly narrow viewpoint, the whole section gives some excellent methods of how clinicians and their management colleagues in trusts should be considering the area of risk management. The arguments are compelling.

Finally, the book ends with a number of appendices on clinical negligence scheme for trusts, Governments proposals for the NHS complaints procedure, potential job descriptions for clinical risk managers and other such useful documentation.

This is an important book for anyone involved in risk management in hospitals in the UK. It can serve as a good reference book, each chapter being well referenced, but it is written well enough to be an interesting and useful read from cover to cover.

A. G. H. Cole

Neuromuscular Transmission. Fundamentals of Anaesthesia and Acute Medicine Series. L. H. D. J. Booij (editor). Published by BMJ Publishing Group, London. Pp. 196; indexed; illustrated. Price £27.95.

This small book is one of a series from the BMJ Publishing Group on the "Fundamentals of Anaesthesia and Acute Medicine". The series aims to update the reader on the principal clinical topics related to anaesthesia: this issue is on neuromuscular transmission. It is edited by Professor Leo Booij (Netherlands) and is written by an international team of well recognized contributors to the field of neuromuscular physiology and pharmacology.

The physiology of neuromuscular function is covered in detail: three chapters consider prejunctional events, postjunctional mechanisms, and perhaps most importantly, the central control of neuromuscular transmission. Such central control is an important factor during general anaesthesia (in contrast with the use of neuromuscular blocking agents in the critically ill), and it is apposite that a full chapter is dedicated to it. It is impossible as yet to give a full explanation of these effects, but recent advances have been detailed and some thought-provoking ideas are given.

As with any multi-author text, the standards vary between chapters and there is some repetition. Several are well referenced, particularly the chapters on drug interactions, non-depolarizing neuromuscular blocking agents, neuromuscular blockers and concurrent disease, and active reversal of neuromuscular block. In addition, these chapters are impressively detailed. How many readers realize that famotidine is the only H_2 receptor antagonist *without* a neuromuscular blocking effect? Or that the aminosteroids were derived from the African poison, *Malouetia bequaertiana*? I certainly did not. The work involved in such an exercise should not be underestimated. Professor Booij is to be congratulated on his efforts; despite the multiple authorship, his contribution is the most impressive.

Undoubtedly, it would be pedantic to mention the small referencing errors which exist throughout the text. There are also some factual errors, however. Pancuronium is certainly *not* one of the most frequently used non-depolarizing neuromuscular blockers in the UK: it has not been so for 15 yr. Only the older generation of anaesthetists now use it: in some hospitals it would be impossible to find. Nor does renal failure cause an exaggerated hyperkalaemic response to suxamethonium: the effect is more marked only because the baseline serum potassium concentration is higher, and therefore toxic concentrations are reached more easily.

I would prefer to have had more information on plasma cholinesterase in this text. Now that its structure has been defined and more is known about the various patterns of inheritance of abnormal cholinesterase, this would have been interesting. More mention of the latest knowledge on malignant hyperthermia and neuromuscular blockers would also have been useful in the concurrent disease chapter.

Nevertheless, every *twitcher* should have this book on their shelves (for the references alone), even though several similar texts are now available on neuromuscular function. We certainly do not need any more until the next millennium. There only remains a need for a tome on the physiology and pharmacology of neuromuscular function; a reference book which covers all aspects of this subject. I wonder who will have the energy to edit it!

J. M. Hunter

British Journal of Anaesthesia 1996;77:566–567

ERRATA

British Journal of Anaesthesia 1996; **76**: 816–821

p. 819. In figures 1 and 2 of this article, the legend identifying the two groups was omitted. These two figures and the correct legends are reproduced below.

We apologize to the authors for this confusion, which arose during the editorial process.

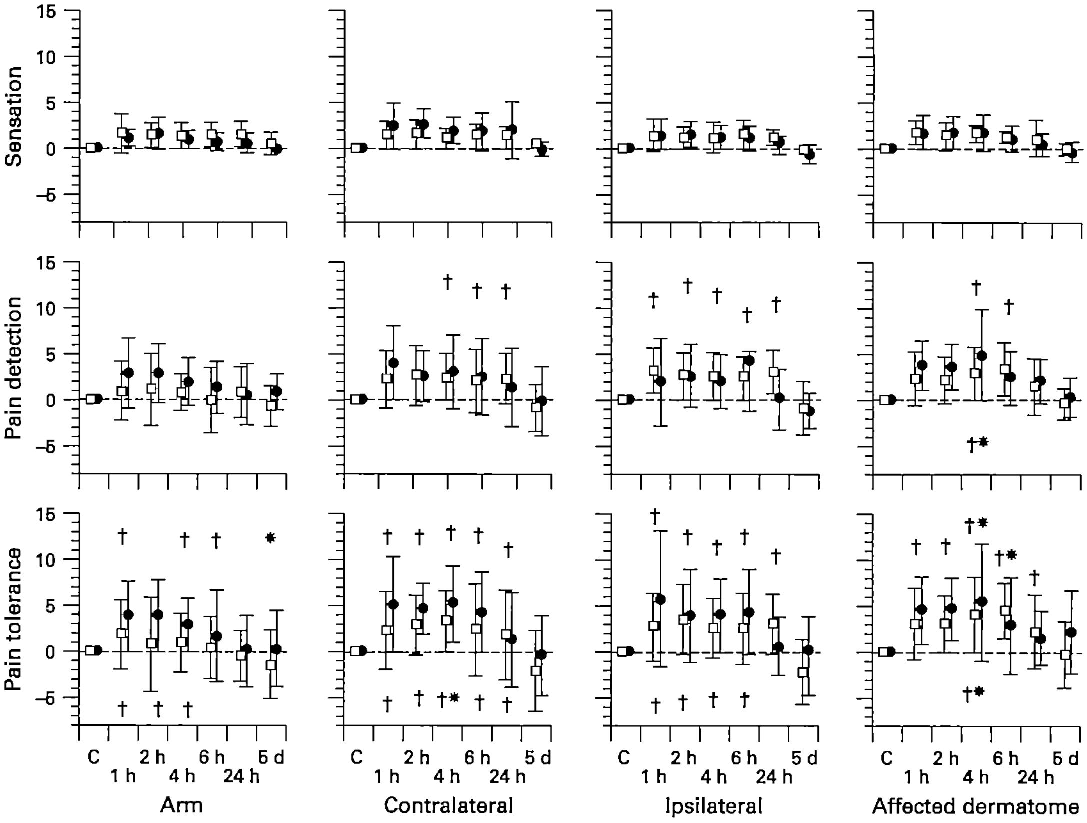

Figure 1 Changes from baseline of raw sensory thresholds (mean, SD mA). The dermatomes tested (X axis) and the types of threshold tests (Y axis) are indicated. $^*P<0.05$ *vs* baseline, $\dagger P<0.05$ *vs* day 5 value. The significances for the placebo group (□) are marked above the zero line, those for the fentanyl group (●), below. Only differences at individual times within a given graph are marked (for other results, see text).

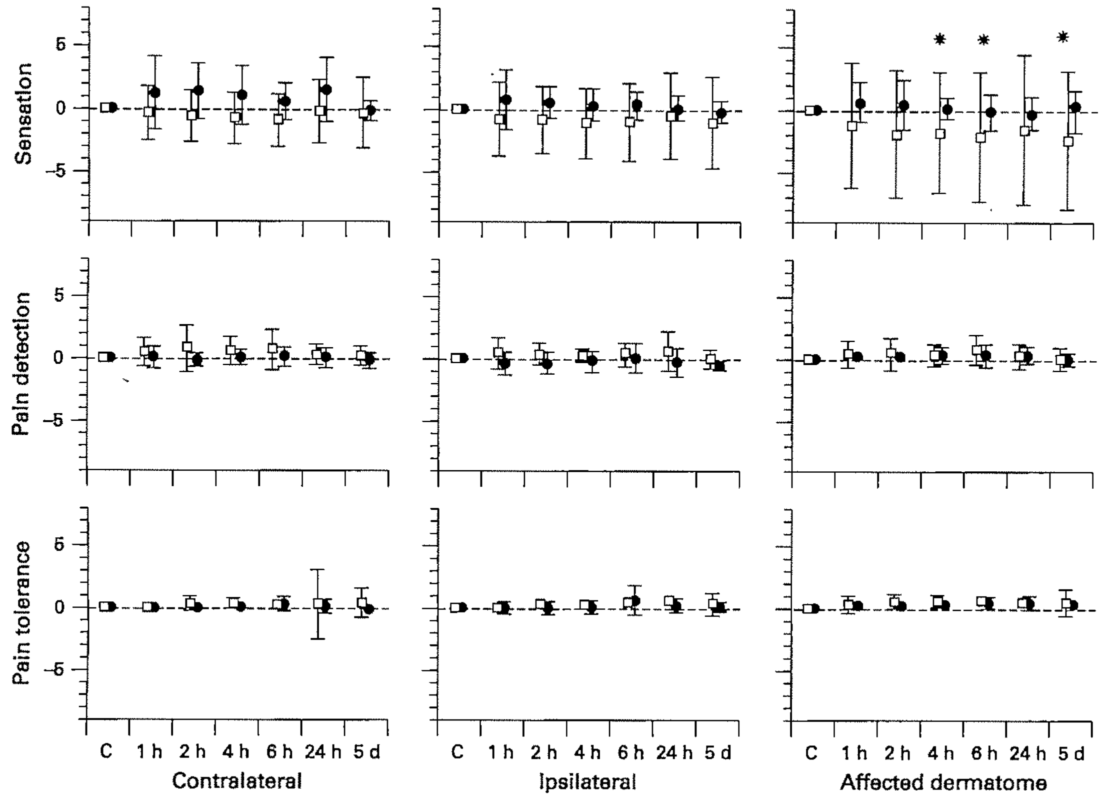

Figure 2 Changes from baseline of normalized sensory thresholds in arbitrary units (mean, SD ratios). The dermatomes tested (X axis) and the types of threshold tests (Y axis) are indicated. *$P<0.05$ *vs* baseline. The significances for the placebo group (□) are marked above the zero line, those for the fentanyl group (●), below. Only differences at individual times within a given graph are marked (for other results, see text).

British Journal of Anaesthesia 1996; **76**: 829–834

p. 831. In figure 2, the filled symbols were omitted and thereby the significance results. The correct figure is reproduced below.

We apologize to the authors for this confusion.

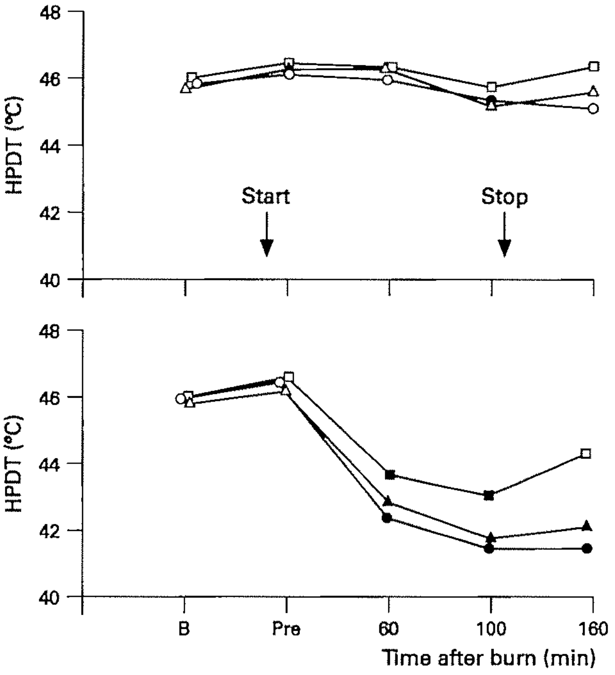

Figure 2 Heat pain detection threshold (HPDT) on the unburned (top) and burned (bottom) calf (medians) before (baseline (B) and before the burn injury (Pre)), during and after infusion of placebo (○), ketamine 0.15 mg kg^{-1} (△) or ketamine 0.30 mg kg^{-1} (□). Start, stop = Beginning and end of infusion of ketamine or placebo. Ketamine 0.15 mg kg^{-1} *vs* placebo: $P>0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P>0.05$, non-parametric two-way analysis for unburned calf; ketamine 0.15 mg kg^{-1} *vs* placebo: $P>0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P<0.05$, non-parametric two-way analysis for burned calf. Filled symbols = significant difference from baseline (Friedman's ANOVA).

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EDITORIAL

Does anaesthesia have long-term consequences?

The definition of anaesthesia as a triad of hypnosis, analgesia and neuromuscular block,[1] now seems simplistic; it ignores other less obvious effects, which may be either beneficial or detrimental to our patients. One example of a more subtle effect of anaesthesia is how it may influence communication between cells. Intact intercellular signalling underlies the ability of an organism to mount an appropriate physiological response to an insult. In many pathophysiological processes, including wound healing, ischaemia and malignancy, defective signalling is known to occur.[2] Progress in basic science has led to the identification of, and the technology to measure, a group of intercellular mediators termed *cytokines*. These comprise a family of small proteins and glycoproteins (molecular weight 15–30 kDa). Under normal conditions, baseline production of cytokines is low, but when triggered by appropriate stimuli, including infection or surgical injury, production can increase markedly.[3] Most cytokines act in an autocrine (i.e. on the producer cell) or paracrine (i.e. on neighbouring cells) manner.[4] A few members of the family, for example tumour necrosis factor-α (TNF-α), interleukin-2 (IL-2), interleukin-6 (IL-6) and transforming growth factor-β (TGF-β) are transported in the blood to act at distant sites, and thus resemble classical hormones. After stimulation by an insult, leucocytes, macrophages and endothelial cells either release stores, or rapidly switch on the synthesis of cytokines. These mediators regulate the activity, differentiation and growth of many types of cell belonging to the inflammatory and immune systems. Generation of transgenic animals, which either over-express or under-express a specific cytokine, has provided a useful tool to help unravel the functions of these mediators.[5]

Severe injury and infection produce well characterized neuroendocrine and metabolic changes in the host. These changes are mediated, at least partly, by cytokines. TNF-α, IL-1β, IL-2, IL-6 and interferon-α cause release of anterior pituitary hormones by acting on the hypothalamus and pituitary glands.[6 7] Although such cytokine responses are generally believed to be beneficial, some individuals develop an excessive or prolonged response, manifested clinically by the systemic inflammatory response syndrome (SIRS).[8] Many animal studies have been published demonstrating improved outcome after inhibition of cytokine responses. Most of this research has focused on sepsis. They conclude that attenuation of cytokine activity after lipopolysaccharide (LPS) administration, or caecal ligation and puncture, increases survival.[9 10] For many reasons, discussed by Yentis in an editorial in this journal, the expected benefit from cytokine manipulation in sepsis has not yet been realized in human studies.[11]

Cytokine responses to surgery have also been studied, particularly IL-1β, IL-6 and TNF-α, which have been shown to increase in proportion to the magnitude of the operation.[12] Although there is a paucity of data on the influence of anaesthetic drugs and techniques on cytokine responses, there is evidence that anaesthesia is capable of modulating these short-term responses. *In vitro* studies have demonstrated that volatile agents can suppress cytokine release from blood cells. Isoflurane inhibits the secretion of TNF-α and IL-1β from LPS-stimulated human peripheral blood monocytes.[13] In another study, sevoflurane and enflurane were found to inhibit TNF-α and IL-1β release from stimulated monocytes, but the release of IL-2 was unaffected.[14] *In vitro* assessment of anaesthesia and cytokine responses has not been restricted to general anaesthetic agents. Lignocaine inhibits the effect of recombinant human granulocyte colony-stimulating factor (rhG-CSF) on human neutrophil function: it reduces rhG-CSF-induced neutrophil superoxide release and down-regulates leucocyte adhesion molecule-1 expression in a dose-dependent manner.[15]

Few studies have been published on how anaesthesia affects *in vivo* cytokine responses to surgery. Crozier and colleagues compared the changes in plasma concentrations of IL-1β and IL-6 after abdominal surgery, using two different anaesthetic techniques.[16] Compared with anaesthesia using isoflurane and nitrous oxide, total i.v. anaesthesia (TIVA) with propofol and alfentanil caused a significantly reduced and delayed increase in IL-6 concentrations. No difference was observed when concentrations of IL-1β were measured. The authors concluded that alfentanil was the agent responsible for suppressing the release of IL-6. The effect of extradural anaesthesia on the IL-6 response to abdominal surgery has also been investigated: although it caused no overall significant change in cytokine concentrations, a delayed increase in IL-6 was noted.[17] Thus, there is evidence that anaesthesia has the potential to attenuate cytokine responses induced by surgical trauma.

For reasons which remain unclear, some individuals develop uncontrolled cytokine responses and could potentially benefit from appropriately timed cytokine inhibition. Until recently it has not been possible to predict which patients are at risk of mounting this excessive cytokine response to surgical injury. However, molecular biology may be able to offer a solution. Polymorphism is the existence in a population of two or more relatively common alleles at a genetic locus. Polymorphism, or variation in DNA sequence, may occur in an extron (coding portion of the gene) and after transcription and translation, result in the production of a defective protein. Equally, polymorphism may occur in an intron (non-coding portion), but still modify gene expression in other subtle ways.[18] For example, polymorphism may lie in the promoter region of the gene, a part of the gene that is important in determining initiation of transcription. Alternatively, polymorphism itself may be unimportant, except as a marker that may be linked to another, as yet unidentified, allelic variation that is responsible for the altered phenotypic response. Although it is accepted that particular genotypes can predispose individuals to long-term risks in response to environmental stress, for example the familial clustering of some types of cancer, until recently there was little evidence that genotype could alter outcome with respect to short-term stress. Stuber and colleagues have recently reported a genomic polymorphism within the TNF locus that influences concentrations of TNF-α and outcome in patients experiencing the short-term stress of severe sepsis.[19] They used the polymerase chain reaction (PCR) to amplify a 782-base pair fragment of genomic DNA, which included the polymorphic site of a restriction endonuclease (NcoI) within the TNF locus. Each patient's genotype was determined after digestion with NcoI and gel electrophoresis. Two TNF alleles, TNFB1 and TNFB2, were identified and correlated with maximum concentrations of TNF-α and outcome. The 42% of patients who were homozygous for TNFB2 had significantly higher concentrations of TNF-α and a worse outcome. This is the first attempt at using a genetic test to predict cytokine responses and outcome, and should be investigated prospectively. In the future it may be possible, using simple blood tests, to predict which patients are likely to mount excessive cytokine responses after major surgery (high responders). Such tests may help anaesthetists to predict outcome or the need for postoperative intensive care. They may also allow us to select the most appropriate anaesthetic, in terms of its ability to modulate cytokine activity, for each patient.

In addition to modulating cytokine responses to surgical injury, anaesthesia may influence the activity of cytokines involved in coincidental pathophysiological processes. Many cytokines have been identified as pivotal mediators in a wide range of chronic processes. Transforming growth factor-β (TGF-β) may be unfamiliar to most anaesthetists, but is an example of a cytokine which is known to be vitally important in the pathogenesis of many long-term disorders, including wound healing, fracture healing and malignancy. When soft tissue is injured, TGF-β is released from degranulating platelets to trigger a cascade of events, including recruitment of inflammatory cells, angiogenesis and the synthesis of collagen.[2] Application of topical TGF-β promotes wound healing in a variety of animal models and the topical application of anti-TGF-β antibodies reduces cutaneous scarring.[20] Interestingly, Amento and colleagues reported that a single dose of TGF-β administered systemically before wounding also enhanced healing.[21] Thus, transient changes in concentrations of TGF-β may have effects on the long-term process of wound healing. If anaesthesia is shown to change TGF-β activity, even for a short albeit critical period, then it could indirectly influence wound healing after surgery. TGF-β is also thought to contribute to fracture healing and embryonic bone formation. Injections of TGF-β onto the periostea of rat parietal bones induced new bone formation.[22]

Systemic administration of TGF-β protects against ischaemia. It was shown to have cardioprotective effects when administered after experimental myocardial infarction in rats.[23] Systemic administration of TGF-β in a model of splanchnic ischaemic–reperfusion injury was also shown to be protective.[24] Growth of most epithelial and lymphoid cells is inhibited by TGF-β. One postulated mechanism whereby cells undergo carcinogenic transformation and escape from normal growth control appears to involve an altered response to the negative regulation of TGF-β. Studies on a TGF-β-responsive human colonic carcinoma cell line implicated TGF-β as an autocrine and paracrine negative regulator of growth, and suggest that loss of response to TGF-β may contribute to tumour progression.[25]

Our understanding of cytokine biology is developing rapidly. Knowledge as to the identification of patients who are prone to mounting abnormal cytokine responses, and the roles of cytokines in the pathogenesis of disease, is increasing at a phenomenal rate. Anaesthesia must contribute to this exciting and expanding area of research. The study of how different anaesthetic agents and techniques affect cytokine concentrations and activity must continue. Certain agents and techniques could prove to be clinically useful in the modulation of cytokine activity in subjects who are high responders and also influence specific disease processes which are regulated by cytokines. Indeed, there may well be more to anaesthesia than sleep!

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References

1. Rees GJ, Gray TC. Methyl-N-propyl ether. *British Journal of Anaesthesia* 1950; 22: 83–92.
2. Sporn MB, Roberts AB. Transforming growth factor-beta. Multiple actions and potential clinical applications. *Journal of the American Medical Association* 1989; 262: 938–941.
3. Daniak N. Cell membrane family of growth regulatory factors. *Progress in Clinical Biological Research* 1990; 352: 49–61.
4. Brouwer A, Parker SG, Hendriks HFJ, Gibbons A, Horan MA. Stimulation of kupffer cells from young and old rats by endotoxin: 1. Induction of eicosanoids and cytokines. *Clinical Science* 1995; 88: 211–217.

5. Tavernier J. Transgenic mice in the study of cytokine function. *International Journal of Experimental Pathology* 1993; **74**: 525–546.
6. Naito Y, Fukata J, Tominaga T, Nakcin Y, Tamai S, Mori K, Imura H. Interleukin-6 stimulates secretion of adrenocorticotrophic hormone in conscious freely moving rats. *Biochemical and Biophysical Research Communications* 1988; **155**: 1459–1463.
7. Moore CM, Desborough JP, Burrin JM, Hall GM. Interleukin-6 and the pituitary response to surgery. *Journal of Endocrinology* 1992; **132S**: 207.
8. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, Goris RJ. Cytokine patterns in patients after major vascular surgery, haemorrhagic shock and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Annals of Surgery* 1993; **218**: 769–776.
9. Zanetti J, Heumann D, Gerain J, Kohler J, Abbet P, Barras C, Lucas R, Glauser MD, Baumgartner JD. Cytokine production after intravenous or peritoneal gram-negative bacterial challenge in mice. Comparative protective efficacy of antibodies to tumor necrosis factor-α and to lipopolysaccharide. *Journal of Immunology* 1992; **148**: 1890–1897.
10. Giroir BP. Mediators of septic shock: new approaches for interrupting the endogenous inflammatory cascade. *Critical Care Medicine* 1993; **21**: 780–789.
11. Yentis SM. Cytokines and sepsis: time for reappraisal. *British Journal of Anaesthesia* 1995; **74**: 119–120.
12. Cruickshank AM, Fraser WD, Burns HJG, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clinical Science* 1990; **79**: 161–165.
13. Sato W, Enzan K, Masaki Y, Kayaba M, Suzuki M. The effect of isoflurane on the secretion of TNF-α and IL-1β from LPS-stimulated human peripheral blood monocytes. *Japanese Journal of Anesthesiology* 1995: **44**: 971–975.
14. Mitsuhata H, Shimizu R, Yokoyama MM. Suppressive effects of volatile anaesthetics on cytokine release in human peripheral blood mononuclear cells. *International Journal of Immunopharmacology* 1995; **17**: 529–534.
15. Ohsaka A, Saionji K, Sato N, Igari J. Local anesthetic lidocaine inhibits the effect of granulocyte colony-stimulating factor on human neutrophil functions. *Experimental Hematology* 1994; **22**: 460–466.
16. Crozier TA, Muller JE, Quittkat D, Sydow M, Wuttke W, Kettler D. Effect of anaesthesia on the cytokine responses to abdominal surgery. *British Journal of Anaesthesia* 1994; **72**: 280–285.
17. Moore CM, Desborough JP, Powell H, Burrin JM, Hall GM. Effects of extradural anaesthesia on interleukin-6 and acute phase response to surgery. *British Journal of Anaesthesia* 1994; **72**: 272–279.
18. Zehnbauer BA, Buchman TG. Clinical molecular genetics and critical care medicine. *Critical Care Medicine* 1996; **24**: 373–375.
19. Stuber F, Peterson M, Bokelmann F, Schade U. A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-α concentrations and outcome of patients with severe sepsis. *Critical Care Medicine* 1996; **24**: 381–384.
20. Shah M, Foreman DM, Ferguson MW. Control of scarring in adult wounds by neutralising antibody to transforming growth factor-beta. *Lancet* 1992; **339**: 213–214.
21. Amento JB, DeGuzman L, Lee WP, Xu Y, McFatridge LL, Beck LS. The systemic administration of TGF-β1 accelerates wound healing. *Journal of Cellular Biochemistry* 1991; **15**: 191.
22. Joyce ME, Jingushi S, Scully SP, Bollander ME. Role of growth factors in fracture healing. *Progress in Clinical and Biological Research* 1991; **365**: 391–416.
23. Lefer AM, Tsao P, Aoki N, Palladino MA. Mediation of cardioprotection by transforming growth factor-beta. *Science* 1990; **249**: 61–64.
24. Karasawa A, Guo JP, Ma XL, Lefer AM. Beneficial effects of transforming growth factor-beta and tissue plasminogen activator in splanchnic artery occlusion and reperfusion in cats. *Journal of Cardiovascular Pharmacology* 1991; **18**: 95–105.
25. Wo SP, Theodorescu D, Kerbal RS, Willson JK, Mulder KM, Humphrey LE, Brattain MG. TGF-beta 1 is an autocrine-negative growth regulator of human colon carcinoma FET cells in vivo as revealed by transfection of an antisense expression vector. *Journal of Cell Biology* 1992; **116**: 187–196.

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CLINICAL INVESTIGATIONS

Sleep after laparoscopic cholecystectomy

S. ROSENBERG-ADAMSEN, M. SKARBYE, G. WILDSCHIØDTZ, H. KEHLET AND J. ROSENBERG

Summary

The sleep pattern and oxygenation of 10 patients undergoing laparoscopic cholecystectomy were studied on the night before operation and the first night after operation. Operations were performed during general anaesthesia and postoperative analgesia was achieved without the administration of opioids. There were no significant changes in the total time awake or the number of arousals on the postoperative night compared with the night before operation. During the postoperative night, we found a decrease ($P = 0.02$) in slow wave sleep (SWS) with a corresponding increase in stage 2 sleep ($P = 0.01$). SWS was absent in four of the patients after operation, whereas in six patients it was within the normal range (5–20% of the night). The proportion of rapid eye movement (REM) sleep was not significantly changed after operation. There were no changes in arterial oxygen saturation on the postoperative compared with the preoperative night. Comparison of our results with previous studies on SWS and REM sleep disturbances after open laparotomy, suggests that the magnitude of surgery or administration of opioids, or both, may be important factors in the development of postoperative sleep disturbances. (*Br. J. Anaesth.* 1996; **77**: 572–575)

Key words
Sleep. Oxygen, saturation. Hypoxaemia. Surgery, laparoscopy.

Sleep disturbances have been described after major abdominal surgery[1–5] and herniorrhaphy[2 6]; the disturbances include decreases in total sleep time, proportion of rapid eye movement (REM) sleep and slow wave sleep (SWS). These changes are most pronounced on the first and second postoperative nights[1–6], with a subsequent rebound on the following nights.[1 3 5 6] The magnitude of surgery (the surgical stress response), the surroundings (noise, nursing procedures, etc.), pain and administration of opioids are all factors that may influence postoperative sleep,[7] but the relative importance of these factors is still unknown.

The aim of this study was to evaluate postoperative sleep in patients undergoing minimally invasive surgery (laparoscopic cholecystectomy) without administration of opioids during the postoperative period.

Patients and methods

The study was approved by the local Ethics Committee and patients participated in the study after giving informed consent. We studied 10 patients (eight females; median age 51 (range 34–72) yr, weight 83 (55–105) kg and height 167 (158–172) cm) undergoing laparoscopic cholecystectomy. None of the patients was receiving regular medication before operation and exclusion criteria included known sleep apnoea syndrome, neurological, cardiac or respiratory diseases, oxygen administration during the study nights and use of sedatives or hypnotics during the past 2 months at home or during hospitalization. All patients underwent elective surgery with no recognized risk factors and received routine postoperative care.

Anaesthesia was induced and maintained with thiopentone, isoflurane, low-dose fentanyl, midazolam, suxamethonium, atracurium and nitrous oxide in oxygen. After operation, including the first postoperative night, all patients received ibuprofen 600 mg every 8 h. Opioids were not used for postoperative analgesia.

Patients were studied in the surgical ward in a quiet single bedroom for 1 night before operation and on the first postoperative night, from 22:00 to 06:00. For sleep staging, patients were monitored with a Somnolog System (Ventec Aps, Hellerup, Denmark)[8] which records continuously the electroencephalogram (EEG) (alpha and delta activity by one-channel EEG—a modified F3-A2 lead), electromyogram (EMG) (electrodes placed under the base of the mandible), single lead ECG, eye and hand movements (by movement sensors placed on the upper eyelid and dorsally on the proximal joint of the left index finger) and noise level (by a standard microphone placed 1 m above the patient's head). Data were stored in the internal memory of the Somnolog with subsequent downloading to a

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personal computer. The variables in the Somnolog were analysed manually for sleep stage using 6-s epochs throughout the night, according to the criteria of Rechtschaffen and Kales.[8 9]

During the study nights, arterial oxygen saturation (Sp_{O_2}) was measured with a pulse oximeter (Nellcor N-200, Nellcor Inc., Pleasanton, CA, USA) with an adhesive finger probe.[10] Sp_{O_2} data were sampled at 1-s intervals into a bedside personal computer with subsequent data print-out the following morning. Episodic hypoxaemia was defined as a decrease in oxygen saturation of more than 4% from baseline occurring within a 2-min period.[11] Analysis of oximetry data was performed without knowledge of the sleep data except when calculating the frequency of hypoxaemic episodes during periods of REM sleep.

For statistical analysis we used the Wilcoxon signed rank test. $P < 0.05$ was considered significant. Group data are given as median (range).

Results

Median duration of surgery was 85 (range 36–100) min. Duration of anaesthesia was 120 (75–140) min, during which the patients received a total of 1500 (600–2000) ml of isotonic saline. During operation, patients received a total dose of fentanyl 0.4 (0.25–0.50) mg. There was no correlation between fentanyl dose and magnitude of change in sleep pattern. None of the patients received perioperative blood tranfusions and none developed postoperative complications.

There were no significant changes in the total time awake or the number of arousals on the postoperative night compared with the night before operation (table 1). During the postoperative night, we found a significant decrease in SWS ($P = 0.02$) with a corresponding increase in stage 2 sleep ($P = 0.01$). SWS was absent in four patients (fig.1), whereas in six patients SWS was within the normal range (5–20% of the night) on the postoperative night. The proportion of REM sleep was not significantly changed after operation (fig.1). One patient showed a postoperative increase in SWS and REM sleep (fig.1).

Mean arterial oxygen saturation (Sp_{O_2}) and number of desaturations were not significantly changed after operation ($P = 0.2$ and $P = 0.5$). In order to assess the relationship between postoperative REM sleep and episodic hypoxaemia, we used the previously defined index of hypoxaemic episodes during REM sleep for individual patients[3] ((number of hypoxaemic episodes in REM sleep divided by total number of hypoxaemic episodes) divided by (REM sleep time divided by total sleep time)) (table 1). Thus an index of 1 indicates that the distribution of hypoxaemic episodes was equal between REM and non-REM sleep corrected for duration of REM sleep, and an index >1 indicates that episodic hypoxaemia was more frequent in REM than in non-REM sleep for that night. If the patient had no REM sleep on the study night, the index was 0. There were no significant changes in this index between the two study nights ($P = 0.67$).

Table 1 Sleep stages and arterial oxygen saturation (median (range)). *$P<0.05$ compared with preoperative night (Wilcoxon test). REM = rapid eye movement sleep; SWS = slow wave sleep; Sx = sleep stage x.
Index of hypoxaemic episodes in REM[3] =

$$\frac{\text{No. of hypoxaemic episodes in REM sleep/}\;\text{Total number of hypoxaemic episodes}}{\text{REM sleep time/Total sleep time}}$$

	Preoperative night	First postoperative night
Total time awake (% of night)	9 (0–33)	13 (0–38)
REM sleep (% of night)	17 (10–31)	14 (0–31)
S1 (% of night)	7 (0–15)	4 (1–7)
S2 (% of night)	45 (28–63)	57 (41–72)*
SWS (S3+S4) (% of night)	13 (2–27)	7 (0–13)*
Arousals (n)	21 (8–34)	15 (7–100)
Mean Sp_{O_2} (%)	95 (94–98)	96 (93–96)
Number of desaturations (n)	10 (2–19)	10 (1–51)
Index of episodes in REM sleep	1 (0–4)	8 (0–51)

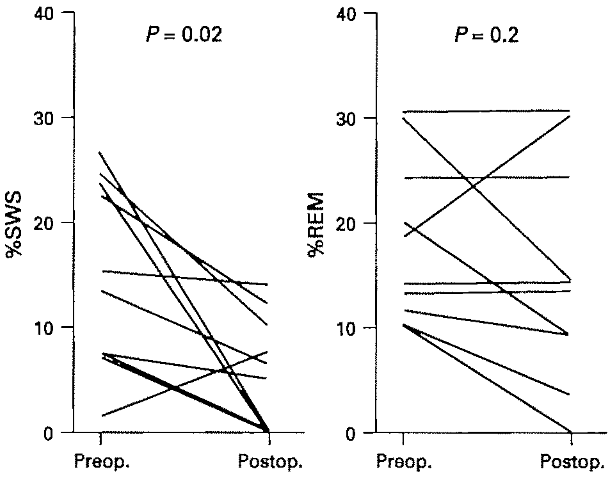

Figure 1 Individual values for the proportion of time spent in slow wave sleep (SWS) and rapid eye movement (REM) sleep on the preoperative and postoperative nights. Values are given as percentages of the study night.

Discussion

This study is the first to describe the sleep pattern after laparoscopic cholecystectomy. We found a slight decrease in SWS, but REM sleep on the first night after operation was unchanged. Also, arterial oxygen saturation (constant and episodic hypoxaemia) was unchanged.

Postoperative sleep disturbances in patients undergoing non-cardiac surgery have been described after major abdominal surgery[1–5] and herniorrhaphy.[2 6] The investigators found a marked reduction in SWS during the first 1–4 postoperative nights,[1–4 6] and in a previous study from our group, SWS was absent in all 10 patients on the first night after major abdominal surgery.[3] In our study there was only a slight decrease in SWS, and in six of our 10 patients, SWS was within the normal range on the first night after operation. It may be argued that recovery from a "first night effect" with impaired sleep on the preoperative night might have contributed to the relatively small changes seen from the preoperative (first night) to the postoperative night. However, we have shown previously that when monitoring surgical patients for 2 nights before operation and with the same monitoring equipment and experimental set-up, a first night effect was not present.[3]

After major surgery, REM sleep is usually absent on the first and sometimes the second and third postoperative nights,[1–6] followed by an increased duration of REM sleep and density (rebound) during the subsequent 2–4 nights.[1 3 5 6] In a previous study, performed after major abdominal surgery, there was a significant decrease from a median of 17% to 5% in the proportion of REM sleep on the first night after operation.[3] In this study, however, there were no significant changes in the proportion of REM sleep after minimally invasive surgery.

Our patients did not have decreased total sleep time. Previous studies in patients undergoing major abdominal surgery or herniorrhaphy have found that total sleep is reduced by up to 80% on at least one of the first postoperative nights,[2 4 6] and fragmented with numerous movement arousals and spontaneous awakenings.[1 2 6] In our study, however, patients were awake for a total of 13% (range 0–38%) of the first postoperative night, but without an increase in the number of arousals on the postoperative compared with the preoperative night (table 1). As sleep duration and fragmentation are important determinants for the subjective restorative capability of sleep,[11] our patients should have been less affected by their postoperative sleep changes than patients undergoing major abdominal surgery or herniorrhaphy, although we did not ask for subjective sleep quality.

The clinical consequences of postoperative sleep changes are unknown, although there may be several potential important implications.[7] Experimental deprivation of SWS produces a feeling of physical discomfort,[12] characterized by a depressive and hypochondriacal reaction.[12] This may contribute to the feeling of fatigue in postoperative patients, although a relationship between postoperative sleep disturbances and postoperative fatigue has yet to be demonstrated.[7] Postoperative REM sleep deprivation may be a factor in the development of postoperative impairment of mental function.[13] The postoperative rebound of REM sleep may contribute to the development of sleep-disordered breathing and nocturnal hypoxaemia,[3 5 7] as episodic hypoxaemia is more frequent in periods of REM rebound than during other sleep stages in the postoperative period.[3 5] Furthermore, postoperative REM sleep rebound may be associated with haemodynamic instability and increased mean arterial pressure.[14 15] In the postoperative period, these haemodynamic changes may be related to hypoxaemic episodes,[3] and the simultaneous decrease in myocardial oxygen supply (hypoxaemia) and increase in myocardial oxygen demand (tachycardia and hypertension) may lead to postoperative myocardial ischaemia[16 17] and infarction.

Several factors may contribute to the disturbed sleep in postoperative patients. The magnitude of surgery seems to be important, as the reduction in REM sleep, SWS and the lack of inherent rhythmicity were more pronounced after major (gastrectomy or vagotomy) compared with minor (hernia repair) surgery.[2] In addition, morphine, in doses of 0.1 and 0.2 mg kg^{-1} i.m. in healthy volunteers, disrupted sleep in a dose-dependent manner.[18] There are no studies on the effect of systemic or extradural morphine on sleep in postoperative patients.

This study has shown a slight decrease in SWS as the only significant sleep disturbance on the first postoperative night in patients undergoing minimally invasive surgery without administration of opioids during the postoperative period, thus supporting the hypothesis that the magnitude of surgery, administration of opioids, or both, may be important factors in the development of postoperative sleep disturbances. The anaesthetic technique *per se* does not appear to be an important factor as similar degrees of sleep disturbances have been found after general or regional anaesthesia for herniorrhaphy[6] or minor surgery.[19] A study in volunteers anaesthetized for 3 h with isoflurane found no significant disturbances in the post-anaesthetic sleep pattern other than a slight decrease in SWS on the first night[20]; this is comparable with the sleep pattern in our patients after laparoscopic cholecystectomy.

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References

1. Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; 73: 52–61.
2. Ellis BW, Dudley HAF. Some aspects of sleep research in surgical stress. *Journal of Psychosomatic Research* 1976; **20**: 303–308.
3. Rosenberg J, Wildschiødtz G, Pedersen MH, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *British Journal of Anaesthesia* 1994; 72: 145–150.
4. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *Bristish Medical Journal* 1985; **290**: 1029–1032.
5. Knill RL, Moote CA, Rose EA, Skinner MI. Marked hypoxemia after gastroplasty due to disorders of breathing in REM sleep. *Anesthesiology* 1987; 67: 3A.
6. Kavey NB, Altshuler KZ. Sleep in herniorrhaphy patients. *American Journal of Surgery* 1979; 138: 682–687.
7. Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. *British Journal of Anaesthesia* 1996; 76: 552–559.
8. Wildschiødtz G, Clausen J, Langemark M. The Somnolog system: home monitoring of sleep-EEG, other physiologic data, and sound pressure level. In: Miles LE, Broughton RJ, eds. *Medical Monitoring in the Home and Work Environment.* New York: Raven Press, 1990; 285–294.
9. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Bethesda, MD: US Department of Health, Education, and Welfare, 1968.
10. Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology* 1989; 70: 98–108.
11. Åkerstedt T, Hume K, Minors D, Waterhouse J. The meaning of good sleep: a longitudinal study of polysomnography and subjective feeling of sleep quality. *Journal of Sleep Research* 1994; 3: 152–158.

12. Agnew HW, Webb WB, Williams RL. Comparison of stage four and 1-REM sleep deprivation. *Perceptual and Motor Skills* 1967; **24**: 851–858.
13. Helton MC, Gordon SH, Nunnery SL. The correlation between sleep deprivation and the intensive care unit syndrome. *Heart and Lung* 1980; **9**: 464–468.
14. Mancia G. Autonomic modulation of the cardiovascular system during sleep. *New England Journal of Medicine* 1993; **328**: 347–349.
15. Somers VK, Phil D, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *New England Journal of Medicine* 1993; **328**: 303–307.
16. Rosenberg J, Rasmussen V, von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG-abnormalities. *British Journal of Anaesthesia* 1990; **65**: 684–691.
17. Gill NP, Wright B, Reilly CS. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. *British Journal of Anaesthesia* 1992; **68**: 471–473.
18. Moote CA, Knill RL, Skinner MI, Rose EA. Morphine disrupts nocturnal sleep in a dose- dependent fashion. *Anesthesia and Analgesia* 1989; **68**: S200.
19. Lehmkuhl P, Prass D, Pichlmayr I. General anaesthesia and postnarcotic sleep disorders. *Neuropsychobiology* 1987; **18**: 37–42.
20. Moote CA, Knill RL. Isoflurane anesthesia causes a transient alteration in nocturnal sleep. *Anesthesiology* 1988; **69**: 327–331.

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Gasless laparoscopic cholecystectomy: comparison of postoperative recovery with conventional technique

A.-M. KOIVUSALO, I. KELLOKUMPU AND L. LINDGREN

Summary

We have compared, in a randomized study in 26 patients, immediate and late postoperative recovery after elective laparoscopic cholecystectomy using the gasless, mechanical abdominal wall lift method with conventional carbon dioxide pneumoperitoneum. After the gasless method, tracheal extubation was performed significantly earlier than after the conventional method ($P < 0.01$). End-tidal carbon dioxide concentrations were significantly higher after pneumoperitoneum for 30 min after operation ($P < 0.01$). In the conventional group, deviation in Maddox–Wing recordings from preoperative values remained at a significantly higher level during the 3-h recovery room period ($P < 0.01$). There was a positive correlation between the total amount of carbon dioxide used and duration of drowsiness ($r = 0.61$, $P < 0.001$) and the Maddox–Wing deviation ($r = 0.62$, $P < 0.001$). Postoperative nausea and vomiting, and right shoulder pain occurred less often after the gasless method ($P < 0.05$). Late recovery criteria (ability to drink, void and walk) in patients in the gasless group were fulfilled approximately 7 h earlier than in those in the pneumoperitoneum group ($P < 0.01$). Gasless laparoscopic cholecystectomy resulted in more uneventful and faster immediate and late postoperative recovery than conventional carbon dioxide pneumoperitoneum. (*Br. J. Anaesth.* 1996; **77**: 576–580)

Key words
Surgery, laparoscopy. Complications, pneumoperitoneum. Recovery, postoperative.

Laparoscopic cholecystectomy has rapidly replaced open cholecystectomy as a standard treatment of symptomatic gallstones. Laparoscopic cholecystectomy restores pulmonary function better and enables less painful recovery, shorter hospitalization and faster return to normal activities than open cholecystectomy.[1] Induction and maintenance of carbon dioxide pneumoperitoneum can, however, have serious adverse physiological effects.[2–11] In addition to peroperative problems, postoperative sequelae are also seen not infrequently.[5] Insufflated carbon dioxide is absorbed into the circulation resulting in hypercapnia.[12] Furthermore, lung ventilation is the only mechanism for elimination of carbon dioxide. After conventional laparoscopic cholecystectomy, postoperative nausea and vomiting (PONV) have been reported in up to 68% of patients.[13 14] After laparoscopic cholecystectomy with combined low-pressure pneumoperitoneum and abdominal wall lift, the incidence of PONV was 8%.[5] In addition, postoperative drowsiness was also of significantly longer duration and right shoulder pain occurred more often after conventional carbon dioxide pneumoperitoneum.[5] Also, the more carbon dioxide used the more restless were patients in the recovery room.

Therefore, we evaluated to what extent a totally gasless method for laparoscopic cholecystectomy would affect the quality of immediate and late postoperative recovery.

Patients and methods

We studied 26 ASA I–II patients undergoing elective laparoscopic cholecystectomy. The study was approved by the local Ethics Committee and informed consent was obtained. Patients were allocated randomly to one of two groups. Patients in one group underwent laparoscopic cholecystectomy with conventional pressure pneumoperitoneum (CPP group) (intra-abdominal pressure (IAP) 12–15 mm Hg) with room temperature carbon dioxide insufflation. In the other group, a retractor (Laparolift TM, Origin Medsystems Inc., USA) (fig. 1) was used to elevate the abdominal wall upwards by 10–15 cm.[15] No carbon dioxide was used (retractor group). All operations were performed by the same experienced senior surgeon (I. K.).

Patients were premedicated with oral diazepam 0.2 mg kg^{-1} approximately 60 min before arrival in the operating theatre. Glycopyrronium 3 $\mu g\ kg^{-1}$ was given i.v. to all patients. Fluid administration of Ringer's acetated solution and hydroxyethyl starch (Plasmafusin, Pharmacia AB, Sweden) was standardized. Anaesthesia was induced with alfentanil 20 $\mu g\ kg^{-1}$ and propofol 1.6–2.5 mg kg^{-1}. Alfentanil 20 $\mu g\ kg^{-1}$ was given before the start of surgery in all patients. Neuromuscular block was provided with

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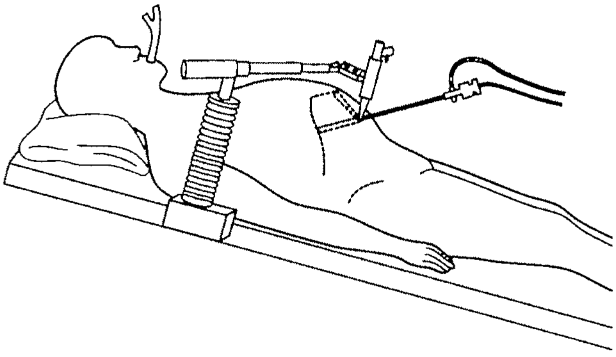

Figure 1 Schematic illustration of the retractor method.

atracurium and was monitored using the train-of-four technique. If the surgeon complained of stiffness of the abdominal muscles an additional bolus of atracurium 10 mg was given. Anaesthesia was maintained with desflurane at an end-tidal concentration of 6.1% (1 MAC) and oxygen in air ($F_{I_{O_2}}$ 0.4). No nitrous oxide was used. The lungs of all patients were ventilated mechanically at 10 bpm (Servo 900 C, Siemens Anmedic, Elema Schönander, Sweden). If needed, minute volume of ventilation was increased to maintain end-tidal carbon dioxide concentration at 4.5–5.0% (AS / 3, Datex Ltd, Finland). Analgesia was achieved with an infusion of alfentanil 10–200 $\mu g\ kg^{-1}\ h^{-1}$ titrated to avoid increases in arterial pressures of more than 20% from the pre-anaesthetic value. The total amount of alfentanil used during anaesthesia was noted and neuromuscular block was not antagonized with neostigmine. After operation, patients were allowed to breathe spontaneously and the trachea was extubated when breathing was regular, end-tidal carbon dioxide was decreasing and laryngeal reflexes had recovered. In all patients, end-tidal desflurane was 1% or less at the time of extubation. The time interval from extubation until patients responded to commands and gave their date of birth was recorded.

After operation patients were followed up for 3 h in the recovery room. Abdominal pain at rest and during coughing, and right shoulder pain were assessed using a verbal rating scale (0–3). If the pain score was 2 or more the patient received oxycodone 0.07 $mg\ kg^{-1}$ i.v. If the pain score remained 2 or more for more than 15 min the dose of oxycodone was repeated and ketorolac 30 mg i.v. was given. End-tidal carbon dioxide concentration was recorded after 1 deep breath hourly using a nose catheter (Cardiocap, Datex Ltd, Finland). Sedation was scored : 0 = fully awake, 1 = sedated, responding to commands, 2 = hardly responding to commands, 3 = not responding to commands. Restlessness was scored : 0 = calm, 1 = little movements all the time, 2 = needs someone to sit beside, 3 = needs sides for the bed. Drowsiness was scored : 0 = brisk, 1 = little tired, 2 = likes to sleep, 3 = does nothing but sleeps. A score of 2 or more was considered as sedation, restlessness or drowsiness. Duration of drowsiness and PONV were observed. Only vomiting was treated with droperidol 0.625 mg i.v. The baseline Maddox–Wing ocular test was performed on the day before operation after careful explanation of the use of the instrument to the patient.[16] Postoperative tests were performed hourly during the 3-h recovery room stay. Changes in the Maddox–Wing recording from the preoperative value were noted. All postoperative recordings were performed by a trained nurse unaware of the method used during operation.

Late recovery was recorded as the interval from tracheal extubation to the moment the patient was voluntarily able to void, drink and walk.

Patients were interviewed on the first day after operation, with special reference to pain and its location and PONV. All drugs needed during the first 27 h after operation were noted.

STATISTICAL ANALYSIS

Data within a group were analysed using one-way analysis of variance (ANOVA) with PLSD correction (least significant test). The differences between the two groups were analysed using two-way ANOVA with PLSD correction or Fisher's exact test for small groups.[17] Calculations were performed using Stat View 512 + TM software (Brain Power Inc., Calabasas, CA, USA). Correlations between the total amount of carbon dioxide and deviation in Maddox–Wing recordings from preoperative value and between duration of drowsiness were calculated. Data are expressed as mean (SD). $P < 0.05$ was considered statistically significant.

Results

The two groups were comparable in age, height, weight, ASA status and sex. Duration of operation was 108 (28) min in the retractor group and 85 (25) min in the CPP group ($P < 0.05$). Total amount of carbon dioxide was 55 (34) litre in the CPP group whereas in the retractor group carbon dioxide was not used ($P < 0.001$). Total amounts of alfentanil and propofol used were comparable in the two groups: in the retractor group 84 (70) $\mu g\ kg^{-1}$ and 2.3 (0.6) $mg\ kg^{-1}$, respectively, and in the CPP group, 104 (76) $\mu g\ kg^{-1}$ and 2.1 (0.4) $mg\ kg^{-1}$, respectively (ns). Atracurium was needed significantly more in the retractor group (1.0 (0.1) $mg\ kg^{-1}$) than in the CPP group (0.8 (0.2) $mg\ kg^{-1}$) ($P < 0.05$) (table 1).

Patients in the retractor group fulfilled the extubation criteria 10 (4) min after discontinuation of desflurane. This value was 23 (15) min in the CPP

Table 1 Patient characteristics, surgical and anaesthesia data (mean (SD or range) or number). CPP = Conventional pressure pneumoperitoneum. *$P < 0.05$, ***$P < 0.001$ between groups

	Retractor group (n=13)	CPP group (n=13)
Age (yr)	41 (27–59)	47 (27–73)
Height (cm)	167 (8)	167 (6)
Weight (kg)	70 (13)	72 (15)
ASA I/II	9/4	9/4
Sex (F/M)	12/1	12/1
Duration of op. (min)	108 (28)*	85 (25)
Total amount of CO_2 (litre)	0***	55 (34)
Atracurium ($mg\ kg^{-1}$)	1.0 (0.1)*	0.8 (0.2)
Alfentanil ($\mu g\ kg^{-1}$)	84 (70)	104 (76)

Table 2 Postoperative characteristics (mean (SD)). $^{*}P < 0.05$, $^{**}P < 0.01$ between groups

	Retractor group (n=13)	CPP group (n=13)
Extubation after discontinuation of anaesthetic (min)	11 (4)**	23 (15)
Skills after extubation		
Co-operation (min)	0.4 (0.4)	3 (4)
Orientation (min)	1 (1)	5 (11)
Able to (h)		
Drink	9 (5)	12 (7)
Void	10 (4)	14 (5)
Walk	11 (5)**	18 (4)
Duration of drowsiness (min)	31 (61)	82 (76)
Number of patients with		
Right shoulder pain	1*	7
Vomiting	1*	8
Doses of oxycodone per patient		
During the first 3 h	2.5 (1.3)	2.1 (1.7)
During the next 24 h	1.7 (1.1)	1.2 (1.2)

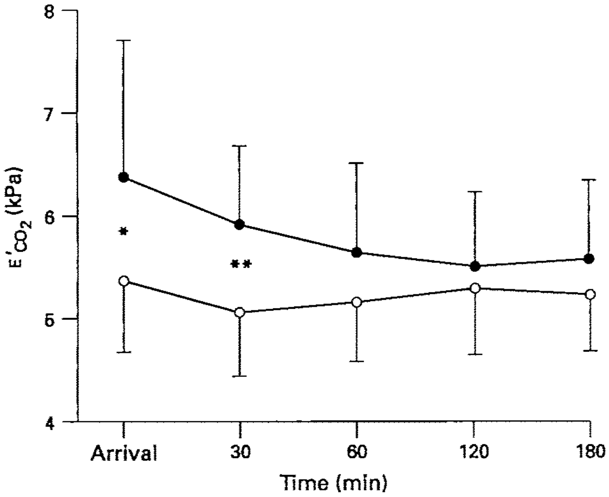

Figure 2 End-tidal carbon dioxide concentration (E'_{CO_2}) during the 3-h recovery room period in the retractor (○) and CPP (●) groups. $^{*}P < 0.05$, $^{**}P < 0.01$.

group ($P < 0.01$). Patients in the retractor group responded to commands 0.4 (0.4) min and gave their date of birth 1 (1) min after extubation. These values were 3 (4) min and 5 (11) min, respectively in CPP group (ns) (table 2).

End-tidal carbon dioxide values in the retractor group were significantly lower compared with those in the CPP group during the first 30 min after operation (fig. 2).

The Maddox–Wing test was recorded in 19 of 26 patients as the remainder were unable to see without spectacles. The deviation in Maddox–Wing recording from the preoperative value was significantly lower in the retractor group than in the CPP group, 2 h after operation ($P < 0.01$) (fig. 3). There was a positive correlation between the total amount of carbon dioxide used and deviation in Maddox–Wing values during the 3-h recovery room period (table 3).

Two patients in the CPP group were so restless that they needed sides for their beds. Amount of carbon dioxide used during operation in these patients was 103 and 40 litre. These two patients and one patient who needed 47 litre of carbon dioxide during operation were sedated (score >2) for the 3-h recovery room period. None of the patients in the retractor group was restless or sedated.

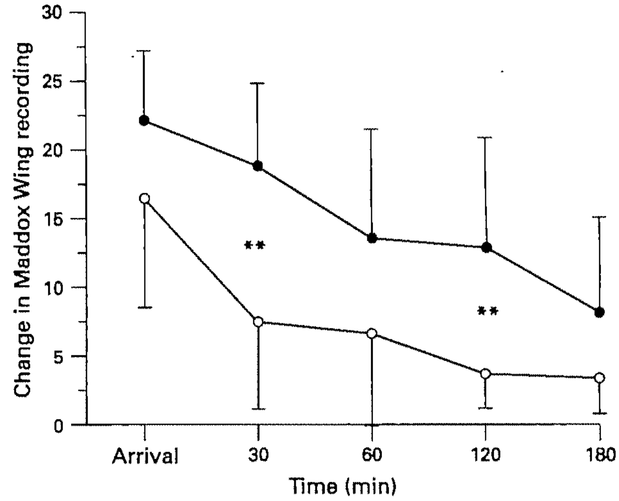

Figure 3 Deviation in Maddox–Wing recording from the preoperative value during the recovery room period in the retractor (○) and CPP (●) groups. $^{**}P < 0.01$.

Table 3 Correlation between the total amount of carbon dioxide used during laparoscopic cholecystectomy and the deviation of the Maddox–Wing test from the preoperative values for 3 h after operation

Time after arrival at recovery room	Correlation coefficient	P
Immediately	0.39	ns
30 min	0.55	< 0.01
60 min	0.5	< 0.01
120 min	0.5	< 0.01
180 min	0.62	< 0.001

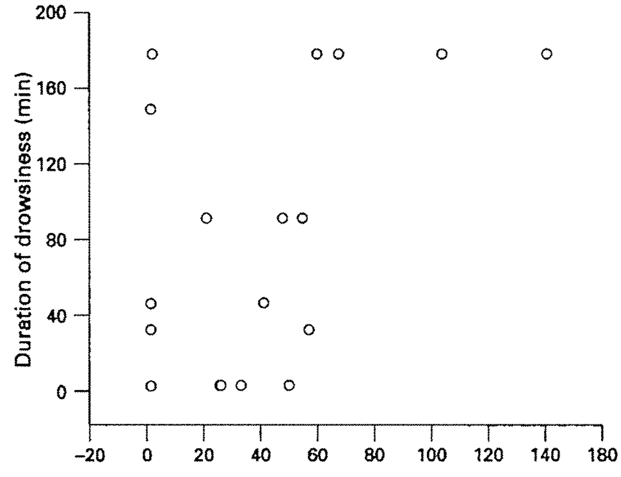

Figure 4 Correlation between duration of drowsiness and total amount of carbon dioxide used during laparoscopic cholecystectomy. $r = 0.61$, $P < 0.01$.

Postoperative drowsiness lasted 31 (61) min in the retractor group and 82 (76) min in the CPP group (ns). There was a correlation between duration of drowsiness and total amount of carbon dioxide used ($r = 0.61$, $P < 0.001$) (fig. 4). In those three patients who were drowsy during the recovery room period, the total amount of carbon dioxide used during laparoscopy was more than 60 litre.

Pain scores and location of the pain during the 3-h recovery room period were similar in both groups. There was no difference in the need for analgesics between groups.

In the recovery room, two patients in the retractor group and five patients in the CPP group needed droperidol for vomiting. During the next 24 h, the groups did not differ in the need for oxycodone (table 2) or ketorolac.

On the first day after operation one patient in the retractor group and seven patients in the CPP group suffered from right shoulder pain ($P < 0.05$). On the first day after operation, eight of 13 patients (62%) in the retractor group described pain in the abdomen "like tenderness after a hard muscle work-out". Pain was unpleasant but not unbearable.

During the next 24 h, one patient in the retractor group and eight patients in the CPP group suffered from vomiting ($P < 0.05$).

Patients in the retractor group were able to drink 9 (5) h after tracheal extubation. In the CPP group this value was 12 (7) h (ns). The interval from extubation to ability to void were 10 (4) h and 14 (5) h, respectively (ns). Patients were able to walk 11 (5) h after extubation in the retractor group and 18 (4) h in the CPP group ($P < 0.01$). In total, seven patients in the retractor group and one in the CPP group fulfilled the late recovery criteria[18] on the evening of the day of operation ($P < 0.05$) (table 2).

There were no perioperative surgical complications.

Discussion

In this study we have shown that postoperative recovery after laparoscopic cholecystectomy was faster and more uneventful when exogenous carbon dioxide was not used. In patients with the gasless method, the trachea was extubated earlier than in those with pneumoperitoneum. They were more often free from PONV and were able to walk earlier than patients after carbon dioxide insufflation.

Atracurium was needed more in the retractor group. This was probably because of the additional need for total relaxation of the abdominal muscles when the abdominal wall was lifted upwards with a force of 10–15 kg. Distension of the abdominal muscles might be painful and explain the similar need for peroperative alfentanil in the two groups. With the conventional method, the need for alfentanil can be explained by the release of endogenous catecholamines.[11]

In our study the duration of drowsiness correlated with the total amount of carbon dioxide used. Exogenous carbon dioxide is absorbed into circulation from the peritoneal cavity during operation and is exhaled via the lungs; this increased end-tidal carbon dioxide concentration occurred in our conventional pressure pneumoperitoneum group up to 1 h after operation. Retention of carbon dioxide might be one reason for prolonged drowsiness. When carbon dioxide is exhaled through the lungs, increased ventilatory drive is needed. In our patients, peroperative infusion of alfentanil was needed for attenuation of the circulatory response to carbon dioxide insufflation, and ventilation was probably inhibited by the residual effects of alfentanil infusion.[19]

The degree of divergence of the small eye muscles measured with the Maddox–Wing device has been found to correlate closely with clinical recovery of patients from general anaesthesia.[16] The Maddox–Wing tests in our patients returned earlier to the baseline level after the retractor method. Because there was a positive correlation between total carbon dioxide used during operation and changes in the Maddox–Wing test, it is probable that the slower recovery of divergence of eye muscles was attributed to the insufflated carbon dioxide. Thus exogenous carbon dioxide may significantly affect progress in early recovery.

PONV occurred significantly more often in patients with carbon dioxide insufflation. Carbon dioxide is a potent vasodilator of cerebral vessels. Increased intracranial blood flow has been seen during laparoscopic procedures.[20 21] Increased intracranial pressure is known to cause nausea and vomiting[22] which may be one reason for PONV in our and in earlier studies.[13 14] Higher end-tidal carbon dioxide concentrations during the 3-h recovery room period in our pneumoperitoneum group may also reflect higher concentrations of carbon dioxide in cerebral blood contributing to the occurrence of PONV. Also, alfentanil causes nausea and vomiting.[23]

Seven patients in the pneumoperitoneum group and only one in the retractor group suffered from right shoulder pain, which is referred pain caused by distension of the right phrenic nerve. Pain in some patients may be severe enough to warrant opioids.[24] In our study, however, the retractor method did not totally abolish right shoulder pain, probably because of diaphragmatic stretching produced by the retractor.

Our patients with the gasless method fulfilled the criteria for late recovery 7 h earlier than those with carbon dioxide pneumoperitoneum. These criteria are commonly accepted for discharge home.[18] More than 50% of patients with the gasless method could be discharged home on the evening of the operation whereas only one patient with carbon dioxide insufflation fulfilled these criteria. Eight patients (62%) in the pneumoperitoneum group needed droperidol for vomiting and required an overnight stay in hospital.

In principle, patients after laparoscopic cholecystectomy can be discharged from hospital on the evening of surgery.[25] However, the use of insufflated carbon dioxide may make this impossible. We suggest that the mechanical abdominal lift method without carbon dioxide insufflation for laparoscopic cholecystectomy may be the method of choice when considering laparoscopic cholecystectomy on a day-case basis.

References

1. McMahon AJ, Russell IT, Baxter JN, Ross S, Andersson JR, Morran CG, Sunderland G, Galloway D, Ramsay G, O'Dwyer PJ. Laparoscopic versus minilaparotomy cholecystectomy: a randomized trial. *Lancet* 1994; 343; 135–138.
2. Noirot D, Joris J, Legrand M, Lamy M. Hemodynamic

changes during pneumoperitoneum for laparoscopic cholecystectomy. *Anesthesiology* 1992; **77**: A69.

3. Odeberg S, Ljungqvist O, Svenberg T, Gannedahl P, Bäckdahl M, von Rosen A, Sollevi A. Haemodynamic effects of pneumoperitoneum and the influence of posture during anaesthesia for laparoscopic surgery. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 276–283.
4. Beebe D, McNevin M, Belani K, Letourneau J, Crain M, Goodale R. Evidence of venous stasis after abdominal insufflation for laparoscopic cholecystectomy. *Anesthesiology* 1992; **77**: A148.
5. Lindgren L, Koivusalo A-M, Kellokumpu I. Conventional pneumoperitoneum compared with abdominal wall lift for laparoscopic cholecystectomy. *British Journal of Anaesthesia* 1995; **75**: 567–572.
6. Diakum TA. Carbon dioxide emboli: successful resuscitation with cardiopulmonary bypass. *Anaesthesiology* 1991; **74**: 1151–1153.
7. McGrath BJ, Zimmerman JE, Williams JF, Parmet J. Carbon dioxide embolism treated with hyperbaric oxygen. *Canadian Journal of Anaesthesia* 1989; **36**: 586–589.
8. Derouin M, Couture P, Boudreault D, Girard D, Gravel D. Detection of gas embolism by transesophageal echocardiography during laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1996; **82**: 119–124.
9. Bardoczky GI, Engelman E, Simon P. Ventilatory effects of pneumoperitoneum monitored with continuous spirometry. *Anaesthesia* 1993; **48**: 309–311.
10. Chang D, Kirsch A, Sawczuk I. Oliguria during laparoscopic surgery. *Journal of Endourology* 1994; **5**: 349–352.
11. Koivusalo A-M, Kellokumpu I, Scheinin M, Tikkanen I, Halme L, Lindgren L. Randomized comparison of the neuroendocrine response to laparoscopic cholecystectomy using either conventional or abdominal wall lift method. *British Journal of Surgery* 1996 (in press).
12. McMahon AJ, Baxter JN, Kenny G, O'Dwyer PJ. Ventilatory and blood gas changes during laparoscopic and open cholecystectomy. *British Journal of Surgery* 1993; **80**: 1252–1254.
13. Thune A, Appelgren L, Haglind E. Prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *European Journal of Surgery* 1995; **161**: 265–268.
14. Koivuranta MK, Läärä E, Ryhanen PT. Antiemetic efficacy of prophylactic ondansetron in laparoscopic cholecystectomy. *Anaesthesia* 1996; **51**: 52–55.
15. Smith RS, Fry W, Tsoi E, Henderson V, Hirvela E, Koeler R, Brams D, Morabito D, Peskin G. Gasless laparoscopy and conventional instruments. *Archives of Surgery* 1993; **128**: 1102–1107.
16. Hannington-Kiff JG. Measurement of recovery from outpatient general anaesthesia with simple ocular test. *British Medical Journal* 1970; **3**: 132–135.
17. Miettinen O. Comment. *Journal of the American Statistical Association* 1974; **69**: 380–382.
18. Korttila K. Recovery from outpatient anaesthesia. *Anaesthesia* 1995; **50**: 22–28.
19. Calvey TN. Side-effect problems of μ and κ agonists in clinical use. In: Budd K, ed. *Update in Opioids. Baillière's Clinical Anaesthesiology. International Practice and Research, vol. 1, No 4*. London, Philadelphia, Sydney, Tokyo, Toronto: Baillière Tindall, 1987; 803– 827.
20. Kirkinen P, Hirvonen E, Kauko M, Purhonen S, Nuutinen L. Intracranial blood flow during laparoscopic hysterectomy. *Acta Obstetricia et Gynecologica Scandinavica* 1995; **74**: 71–74.
21. Fujii Y, Tanaka H, Tsuruoka S, Toyooka H, Amaha K. Middle cerebral arterial flow velocity increases during laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1994; **78**: 80–83.
22. Andrews PLR. Physiology in nausea and vomiting. *British Journal of Anaesthesia* 1992; **69**: (Suppl. 1): 2S–19S.
23. White P, Coe V, Shafer A, Sung ML. Comparison of alfentanil with fentanyl for outpatient anesthesia. *Anesthesiology* 1986; **64**: 99–106.
24. Scheinin B, Kellokumpu I, Lindgren L, Haglund C, Rosenberg PH. Effects of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 195–198.
25. Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1996; **82**: 44–51.

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Haemodynamic and metabolic response to endovascular repair of infra-renal aortic aneurysms

B. R. BAXENDALE, D. M. BAKER, A. HUTCHINSON, T. A. M. CHUTER, P. W. WENHAM AND B. R. HOPKINSON

Summary

We have examined whether or not endovascular insertion of a bifurcated aorto–iliac graft resulted in greater intraoperative haemodynamic and metabolic stability than that achieved during conventional open graft placement. We studied 20 patients prospectively during surgery for asymptomatic infra-renal aortic aneurysm. All patients received the same anaesthetic technique. Haemodynamic data were collected continuously using indwelling radial artery and pulmonary artery catheters, allowing calculation of mean arterial pressure (MAP), cardiac output (CO) and systemic vascular resistance (SVR). Blood samples were obtained for measurement of serum lactate concentrations. Variables were compared within each group before and after specific critical events, namely occlusion of femoral or aortic blood flow, or both, and sequential reperfusion of each lower limb. Patients undergoing open repair showed significant changes in CO, MAP and SVR related to aortic cross-clamping and lower limb reperfusion, and a significant increase in blood lactate concentration after distal tissue reperfusion. The only significant changes during endovascular repair were a transient increase in SVR secondary to application of the femoral artery clamps, and sequential decreases when each limb was reperfused. Endovascular aneurysm repair imposed significantly less intraoperative haemodynamic and metabolic stress on the patient compared with conventional open surgery. (*Br. J. Anaesth.* 1996; **77**: 581–585)

Key words
Surgery, vascular. Arteries, aorta. Cardiovascular system, effects. Metabolism, lactate.

Elective repair of abdominal aortic aneurysms (AAA) by conventional surgery is associated with a mortality of 5–10%, although particular factors such as age and extent of co-existing systemic disease may place patients at much greater risk, even to the extent of denying them surgery. Myocardial infarction (MI) is responsible for 40–70% of this mortality,[1] with infarction within the 6 months preceding surgery and the presence of congestive cardiac failure representing the two most consistent preoperative predictors of perioperative cardiac morbidity. Endovascular repair of AAA is a technique developed to allow exclusion of the aneurysm from the circulation by means of a transfemoral approach. Early experiences with endovascular graft insertion have been reported from Nottingham and other centres.[2–4] This technique offers several potential advantages over conventional (open) repair, including a surgical approach via groin incisions rather than laparotomy, avoidance of retroperitoneal dissection and a much briefer period of abrupt aortic occlusion during placement of the graft. These theoretical advantages are likely to be of benefit to the patient only if they are accompanied by a reduction in the haemodynamic and metabolic stresses imposed by surgery, although the association between these intraoperative improvements and a reduction in postoperative morbidity and mortality may only become apparent by studying large numbers of patients.

We have compared specific intraoperative haemodynamic and metabolic variables in two groups of patients undergoing repair of infra-renal AAA by either open or endovascular surgical techniques.

Patients and methods

After obtaining approval from the hospital Ethics Committee, we studied 20 consecutive adult patients undergoing repair of an infra-renal AAA. Ten patients were selected for insertion of a bifurcated "Chuter" graft by the endovascular technique (endovascular group), with the other 10 patients undergoing conventional graft insertion (open group). Selection into the endovascular group was based primarily on radiographic criteria using calibrated aortic angiography and spiral computed tomograms.[5] This was to ensure that the aneurysm morphology was suitable for the technique, that is a maximum aneurysm proximal neck diameter of 2.5 cm and common iliac diameter of 1.5 cm, minimum

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neck length of 1.5 cm from the origin of the more distal renal artery and relatively non-tortuous iliac artery to permit introduction of the 22-Fr delivery system. Preoperative assessment was standard in both groups, including height, weight, cardiac and pulmonary function and risk factors, hepatic and renal function, and diabetic status. All patients underwent transthoracic echocardiography and spirometry, and had measurement of arterial blood-gas tensions while breathing room air.

All patients were premedicated with temazepam 20 mg orally. A standard anaesthetic technique was used for both groups: i.v. induction with etomidate 0.3 mg kg^{-1}, maintenance with isoflurane and 66% nitrous oxide in oxygen, vecuronium to facilitate tracheal intubation and subsequent ventilation of the lungs, and repeated increments of fentanyl 1–3 μg kg^{-1} for analgesia. No regional anaesthetic technique was used during the intraoperative period. Monitoring included continuous 5-lead electrocardiogram with ST-segment analysis on lead II, and continuous inspired and expired gas analysis for measurement of oxygen, nitrous oxide, carbon dioxide and isoflurane concentrations. Direct continuous measurement of arterial pressure was undertaken via a radial artery cannula, and a pulmonary artery catheter was sited to measure central venous and pulmonary artery wedge pressures. Cardiac output (CO) and systemic vascular resistance (SVR) were calculated at 30-s intervals and displayed on a Baxter Vigilance Monitor (Model VMS) attached to the pulmonary artery catheter.

For the endovascular procedure both common femoral arteries were exposed and heparin 10 000 u. administered i.v. before making bilateral arteriotomies to gain access to the lumen. At this stage both femoral arteries were cross-clamped. A transfemoral catheter was introduced from the left femoral artery and passed over the aortic bifurcation and pulled out of the right femoral arteriotomy with the assistance of a stone retrieval basket. The delivery system comprising an inner shaft and an outer sheath containing the graft and stent was introduced via the right femoral arteriotomy. Particular care was required in deploying the top stent between the renal artery and the aneurysm neck, which was achieved by withdrawing the outer sheath while the inner shaft was stabilized in the correct position assessed by angiographic screening. Complete withdrawal of the outer sheath exposed a catheter attached to the left limb of the graft, which was subsequently sutured to the transfemoral catheter. The left graft limb was guided into the left iliac artery as the transfemoral catheter was withdrawn out of the left femoral arteriotomy. After deployment of both graft limbs, Wallstents (Schneider Ltd) were used to provide additional support. At this stage the femoral artery cross-clamps were removed sequentially and haemostasis secured.

Intravascular volume was supplemented if required with 0.9% sodium chloride solution and modified 4% gelatin solution, volumes administered being guided by reference to the pulmonary artery wedge pressure. If estimated blood loss exceeded 20% of the calculated blood volume, red cell preparations were transfused to replace further losses. Neither group received i.v. mannitol, dopamine or any specific vasoconstrictors, vasodilators or other inotropic support during surgery. The endovascular group received 300–500 ml of non-ionic contrast medium during surgery to allow digital subtraction imaging which ensured accurate deployment of the prosthesis.

Baseline haemodynamic values were obtained after general anaesthesia had been established, before any surgical intervention. Haemodynamic data were collected also throughout surgery with particular reference to a number of critical events: immediately before and after femoral artery clamping (in the endovascular group), immediately before

Table 1 Patient data (mean (range) or number of patients)

	Open group (n=10)	Endovascular group (n=10)
Age (yr)	72.9 (64–83)	68.5 (55–81)
Weight (kg)	77.5 (61–95)	77.3 (58–98)
Sex (M/F)	9/1	9/1
Cardiovascular pathology (see below)	4	6
Respiratory pathology	0	0
Renal impairment (serum creatinine > 150 μmol $litre^{-1}$)	2	1

Cardiovascular pathology (Goldman's risk factors in bold[15])

Each patient is listed numerically. Concurrent cardiovascular medication is shown in parentheses

Open group

1. Echocardiograph: segmental wall dyskinesia, but overall, left ventricular function reasonable
2. Paroxysmal supraventricular tachycardia (flecainide)
3. Coronary artery bypass grafts (CABG) 3 months previously
4. Hypertension (atenolol)

Endovascular group

1. **Atrial fibrillation (AF)**, hypertension, CABG 3 years previously (atenolol)
2. **AF, controlled congestive cardiac failure (CCF)**, myocardial infarct (MI) 3 years previously, angina, hypertension (isosorbide mononitrate (ISMN), diltiazem, GTN patch, enalapril, frusemide)
3. MI 1 year previously, angina, echocardiograph: segmental wall dyskinesia, but overall left ventricular function good (ISMN, nifedipine, atenolol)
4. Hypertension (atenolol)
5. MI 5 years, hypertension (atenolol)
6. Hypertension (nifedipine)

Table 2 Intraoperative details (mean (range)). Data were compared between groups using the unpaired Student's t test. *Open group: time from placement of the aortic cross-clamp until subsequent reperfusion via each prosthetic graft limb; endovascular group: time from placement of each femoral artery clamp until its subsequent release after prosthetic graft insertion

	Open group	Endovascular group	P
Duration of surgery (min)	134.5 (112–192)	142.5 (115–210)	ns
Duration of complete aortic occlusion (min)	52.1 (40–80)	9.2 (6–15)	<0.01
Duration of distal tissue ischaemia* (min)			
First limb	52.1 (40–80)	112.5 (85–160)	<0.01
Second limb	73.5 (53–100)	119.5 (94–166)	<0.01
Blood loss (ml)	1403 (680–2400)	515 (300–750)	<0.01
Fluids administered (ml)			
Crystalloid	2200 (2000–3000)	1690 (1500–2000)	ns
Colloid	950 (500–1000)	550 (0–1000)	<0.01
Red cell preparations	1190 (0–2800)	245 (0–1050)	<0.001
Contrast media	Nil	350 (300–500)	

and after aortic occlusion, and before and after reperfusion of the first and then the second limb. Blood lactate concentrations were measured in both groups at the same times, with samples obtained in sodium fluoride/potassium oxalate bottles and refrigerated until analysis. Haemodynamic variables and blood lactate concentrations were compared within each group during the course of surgery using ANOVA and Student's paired t test ($P < 0.05$). Comparison of blood lactate concentrations was also made between the groups using the Student's unpaired t test ($P < 0.05$).

Results

Patient data for the two groups are summarized in table 1. Details of the duration of surgery, aortic occlusion time, femoral artery clamp time and blood loss are shown in table 2. No patient in the endovascular group required conversion of the technique to an open procedure.

Changes in haemodynamic variables during surgery are shown in figures 1–3. On cross-clamping the aorta in the open group, there were significant increases in mean arterial pressure (MAP) from a mean value of 98 (SEM 6) to 115 (9) mm Hg, and SVR from 2413 (189) to 2660 (204) dyn s cm^{-5}, with CO decreasing from 3.8 (0.4) to 3.0 (0.5) litre min^{-1}. There were no significant changes in the endovascular group when deploying the proximal end of the stent within the aorta. However, the endovascular group demonstrated a significant increase in SVR from 2280 (196) to 2485 (240) dyn s cm^{-5} related to occlusion of blood flow through both femoral arteries. Femoral artery occlusion did not result in significant changes in MAP or CO.

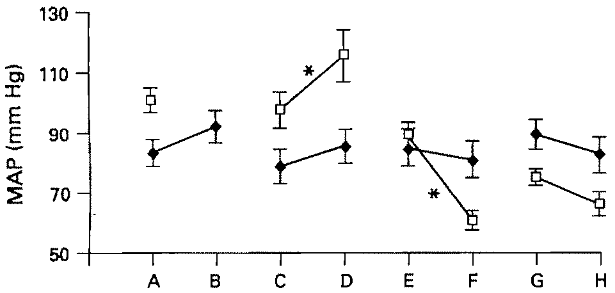

Figure 1 Intraoperative changes (mean, SEM) in mean arterial pressure (MAP) in the open (□) and endovascular (◆) groups. Point A = baseline value for each group. A→B = before and after femoral artery clamping (no data point at B in the open group); C→D = before and after aortic flow occlusion; E→F = before and after reperfusion of the first limb; G→H = before and after reperfusion of the second limb. *$P<0.05$ compared with previous datum point ("within-group comparison" using paired Student's t test).

On reperfusing the first limb, the open group demonstrated significant decreases in MAP from 89 (4) to 61 (3) mm Hg, and SVR from 2327 (146) to 1686 (153) dyn s cm^{-5}, without significant changes in CO. Reperfusion of the second limb caused a further significant decrease in SVR from 1919 (182) to 1586 (152) dyn s cm^{-5}, while MAP and CO remained relatively stable. The only significant changes in the endovascular group were a decrease in SVR from 2104 (167) to 1960 (184) dyn s cm^{-5} when reperfusing the first limb, with a more marked decrease in SVR from 2039 (227) to 1673 (209) dyn s cm^{-5} when the second limb was reperfused. Blood lactate concentrations did not change significantly in either group before reperfusion of distal tissue (fig. 4). Immediately after reperfusing the first limb in the open group, blood lactate concentrations increased from 1.6 (0.2) to 2.4 (0.4) mmol $litre^{-1}$, with a further increase from 2.2 (0.3) to 2.9 (0.4) mmol $litre^{-1}$ when the second limb was reperfused. There were no significant changes in blood lactate concentrations in the endovascular group during reperfusion of either limb.

Two patients in the open group had episodes of fast atrial fibrillation (ventricular response greater than 120 beat min^{-1}) in the first 24-h postoperative period, each requiring pharmacological intervention. There was no significant cardiac morbidity in the first 30 days after operation in the endovascular

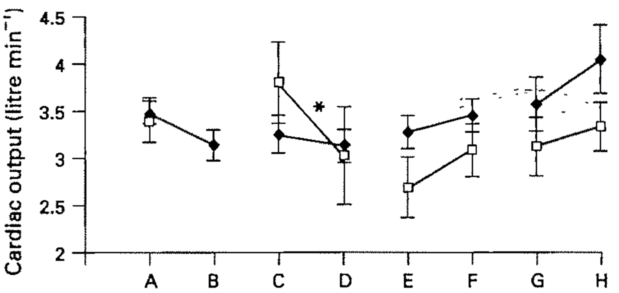

Figure 2 Intraoperative changes (mean, SEM) in cardiac output (CO) in the open (□) and endovascular (◆) groups. Legend and X axis categories are the same as in figure 1.

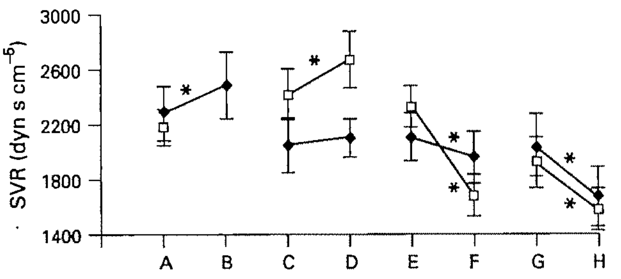

Figure 3 Intraoperative changes (mean, SEM) in systemic vascular resistance (SVR) in the open (□) and endovascular (◆) groups. Legend and X axis categories are the same as in figure 1.

group. There was no cardiac mortality in either group during the same period.

Discussion

We have demonstrated that endovascular exclusion of infra-renal AAA is associated with fewer acute haemodynamic and metabolic changes in the intraoperative period compared with conventional surgery. Cardiovascular and metabolic variables are known to alter significantly during open repair because of abrupt occlusion of blood flow via the aorta caused by cross-clamping, and again when perfusion to the distal tissues is re-established.

Previous studies examining the haemodynamic changes during open repair of AAA have identified aortic cross-clamping as one of the critical intraoperative events, producing up to a 35% decrease in cardiac index and stroke volume, a significant increase in MAP, and a 40% increase in SVR.[6 7] Similar changes were observed in patients in our open group, with SVR increasing by nearly 11%, MAP increasing by 19% and CO decreasing by 21%. The equivalent stage of surgery in the endovascular group was taken to be during deployment of the proximal end of the graft and stent within the aorta. This produced occlusion to aortic flow until the ipsilateral leg of the graft was opened, but this period of complete occlusion lasted for a mean of 9.2 min, significantly less than the 52.1 min during open procedures. Patients in the endovascular group showed greater haemodynamic stability during this period, with predictable but non-significant changes in all variables measured. Several reasons for this may be suggested, in addition to reduction in complete occlusion time. The action of aortic occlusion may have been associated with less notable changes in cardiac output because these patients had already been subjected to prior application of bilateral femoral artery clamps, after which a 22-Fr delivery system was present constantly within the distal aorta and common iliac artery, producing an increase in resistance to blood flow. At the time of proximal graft/stent deployment, we conclude that the endovascular technique resulted in a less profound increase in myocardial afterload and a less marked reduction in preload, both of which have been implicated in the changes seen with aortic cross-clamping during conventional surgery.

Patients in the endovascular group showed a significant increase in SVR secondary to femoral artery clamping during the initial stage of surgery.

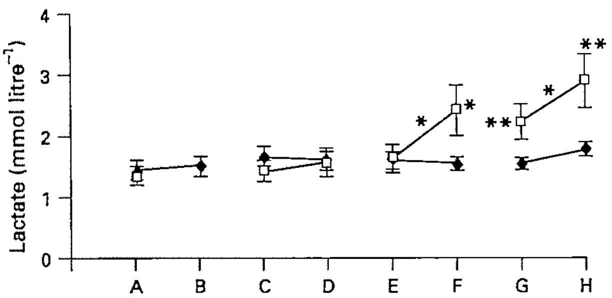

Figure 4 Intraoperative changes (mean, SEM) in blood lactate concentration in the open (□) and endovascular (◆) groups. Legend and X axis categories are the same as in figure 1. $^{**}P < 0.05$ (between-group comparison using unpaired Student's *t* test).

Although there was an associated decrease in CO and increase in MAP, neither change was statistically significant. Subsequent to femoral artery clamping, an angiographic catheter was introduced to allow intraoperative identification of the aneurysm morphology. During this stage SVR returned to baseline values, implying that femoral artery clamping produced a transient effect on the haemodynamic profile, which was relatively non-significant in clinical terms. After positioning the angiographic catheter, the wide-bore co-axial delivery system containing the graft and stents was introduced unilaterally via the femoral and common iliac artery and fed into the aorta beyond the neck of the aneurysm. This stayed in place until the prosthesis was ready for deployment. No significant haemodynamic disturbance resulted from this procedure. No comparative data from the open group were available during this period because of the differences in surgical technique.

Re-establishment of blood flow to tissues distal to an arterial clamp site has two effects: first, decrease in SVR as a result of perfusion of a maximally vasodilated vascular bed; second, return to the circulation of vasoactive metabolic products which have accumulated within the ischaemic tissue. Patients undergoing conventional surgery in our study demonstrated marked haemodynamic changes when the distal tissues were reperfused. Re-establishment of blood flow through the first graft limb produced significant decreases in MAP and SVR, with a further decrease in SVR when the second limb was reperfused. Cardiac output increased during these events, although this was not significant, presumably to compensate to some degree because of maintenance of an adequate left ventricular preload during this period.[6] There was a marked increase in blood lactate concentration in the open group on reperfusion of each limb; reperfusion of the second limb resulted in a 114% increase compared with the baseline value.

In contrast, patients in the endovascular group showed a small but significant decrease in SVR after release of the first femoral clamp, but with rapid recovery towards the pre-release value. A more marked decrease was apparent on release of the second clamp. Each occasion was associated with non-significant changes in MAP and CO. These results suggest that sequential reperfusion via each femoral artery re-opens a vascular compartment sufficient to decrease afterload significantly, but the patient is able to compensate by modest changes in CO, so preventing a clinically significant alteration in MAP. The endovascular group demonstrated no changes in blood lactate concentrations throughout surgery, implying that any "ischaemic" period did not cause a significant metabolic insult from imposed anaerobic metabolism. We suggest that the differences between the two groups related to reperfusion occurred because although the open group had apparently been subjected to a shorter overall period of tissue ischaemia, the quantity and location of tissue rendered ischaemic was significantly different. The endovascular technique used bilateral femoral artery clamps for the majority of surgery, but blood flow through internal iliac and deep femoral collaterals would have continued during this period of arterial clamping.

Haemodynamic stability during endovascular aortic surgery demonstrated in this study represents a potential improvement for patients requiring aortic aneurysm surgery. A significant proportion of this patient population have associated cardiovascular disease, notably previous myocardial infarct (40–50%), congestive cardiac failure (10–15%), ischaemic heart disease (20–30%) or hypertension (50–60%).[8 9] Although debate continues on the combination of preoperative factors associated most reliably with perioperative cardiac morbidity or mortality,[10] it seems reasonable to suggest that a more stable intraoperative haemodynamic profile without evidence of ischaemic metabolic insult may be beneficial during surgery of this type. The Chuter graft/stent system used in this study uses self-expanding modified Gianturco Z-stents, and requires neither deliberate haemodynamic manipulation by the anaesthetist nor balloon inflation at the time of proximal graft fixation, in contrast with other endovascular systems.[4 11] Although the association between improved intraoperative haemodynamic stability and a reduction in significant perioperative cardiac events is intuitive, this study and others to date include insufficient numbers to make firm conclusions.[12] This will rely on larger scale, prospective, randomized, controlled studies being conducted, stating clearly the type of endovascular system being evaluated, with details of preoperative assessment of the patient and perioperative haemodynamic management.[13] This is of paramount importance if the technique is to be considered for patients regarded as representing too high a risk for conventional surgical intervention,[4 14] especially as there is a reported failure rate of approximately 20% in centres experienced with the technique, the consequences of which usually require surgery to be converted to a more extensive procedure or even open repair.[3 4]

References

1. Jamieson WRE, Janusz MT, Miyagishima RT, Gerein AN. Influence of ischaemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation* 1982; **66**: 92–97.
2. Yusuf SW, Baker DM, Chuter TA, Whitaker SC, Wenham PW, Hopkinson BR. Transfemoral endoluminal repair of abdominal aortic aneurysm with bifurcated graft. *Lancet* 1994; **344**: 650–651.
3. May J, White GH, Yu W, Waugh RC, Stephen MS, McGahan T, Harris JP. Surgical management of complications following endovascular grafting of abdominal aortic aneurysms. *European Journal of Endovascular Surgery* 1995; **10**: 51–59.
4. Parodi JC. Endovascular repair of abdominal aortic aneurysms and other arterial lesions. *Journal of Vascular Surgery* 1995; **21**: 549–557.
5. Yusuf SW, Whitaker SC, Baker DM, Chuter TAM, Gregson RHS. Endoluminal repair may be possible in the majority of aneurysms. *British Journal of Surgery* 1995; **82**: 548–563.
6. Silverstein PR, Caldera DL, Cullen DJ, Davison JK, Darling C, Emerson CW. Avoiding the hemodynamic consequences of aortic cross-clamping and unclamping. *Anesthesiology* 1979; **50**: 462–466.
7. Attia RR, Murphy JD, Snider M, Lappas D, Darling C, Lowenstein E. Myocardial ischaemia due to infra-renal aortic cross-clamping during aortic surgery in patients with severe coronary artery disease. *Circulation* 1976; **53**: 961–965.
8. Cunningham AJ. Anaesthesia for repair of abdominal aortic aneurysms. In: Atkinson RS, Adams AP, eds. *Recent Advances in Anaesthesia and Analgesia*. Edinburgh: Churchill Livingstone, 1992; 49–69.
9. Johnston KW. Multicenter prospective study of non-ruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. *Journal of Vascular Surgery* 1989; **9**: 437–447.
10. Mangano DT, Goldman L. Pre-operative assessment of patients with known or suspected coronary disease. *New England Journal of Medicine* 1995; **333**: 1750–1756.
11. Nasim A, Sayers RD, Thompson MM, Bell PRF. Endovascular repair of abdominal aortic aneurysms. *Hospital Update* 1995; 3: 131–135.
12. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischaemia with cardiac morbidity and mortality in men undergoing non-cardiac surgery. *New England Journal of Medicine* 1990; **323**: 1781–1788.
13. Veith FJ, Abbott WM, Yao JST, Goldstone J, White RA, Abel D, Dake MD, Ernst CB, Fogarty TJ, Johnston KW, Moore WS, van Breda A, Sopko G, Didisheim P, Rutherford RB, Katzen BT, Craig Miller D. Guidelines for development and use of transluminally placed endovascular prosthetic grafts in the arterial system. *Journal of Vascular Surgery* 1995; **21**: 670–685.
14. Sayers RD, Thompson MM, Bell PR. Endovascular stenting of abdominal aortic aneurysms. *European Journal of Vascular Surgery* 1993; 7: 225–227.
15. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE. Multifactorial index of cardiac risk in non-cardiac surgical procedures. *New England Journal of Medicine* 1977; **297**: 845–850.

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Comparison of caudal bupivacaine and diamorphine with caudal bupivacaine alone for repair of hypospadias

A. A. KELLEHER, A. BLACK, S. PENMAN AND R. HOWARD

Summary

Forty-five boys undergoing repair of hypospadias were allocated randomly to one of two groups. After induction of anaesthesia, 22 patients received 0.25% caudal bupivacaine 0.5 ml kg^{-1} and diamorphine 30 μg kg^{-1} and the remaining 23 patients received 0.25% caudal bupivacaine 0.5 ml kg^{-1} alone. Pain scores (Children's Hospital of Eastern Ontario Pain Scale), sedation scores, ventilatory frequency, analgesic requirements and associated side effects were recorded for the first 24 h after operation. The two groups were indistinguishable in age, weight and duration of surgery. There was a statistically significant reduction in early pain scores. There was also a statistically significant increase in the time to first passage of urine in those boys in the diamorphine group who were not catheterized during operation. (*Br. J. Anaesth.* 1996; **77**: 586–590)

Key words

Surgery, urological. Anaesthetics local, bupivacaine. Analgesics opioid, diamorphine. Anaesthetic techniques, regional, caudal.

Adequate postoperative analgesia in children is a vital part of perioperative care. Regional techniques such as caudally administered local anaesthetics have long been used in conjunction with general anaesthesia to provide intraoperative and postoperative analgesia. More recently several studies have examined the effects of adding morphine or fentanyl to caudally administered local anaesthetic, some of which appeared to show an improvement in postoperative analgesia. However, at least one case was associated with unacceptable side effects.[1] The aim of this study was to assess the potential benefits and complications associated with adding diamorphine to caudally administered bupivacaine in boys undergoing repair of hypospadias under general anaesthesia.

Patients and methods

After obtaining hospital Ethics Committee approval, informed parental consent was obtained from 45 ASA I and II boys, aged 6–88 months, undergoing repair of hypospadias.

Patients were prescribed premedication with atropine 40 μg kg^{-1} orally and either trimeprazine 3 mg kg^{-1} or temazepam 0.5 mg kg^{-1} orally. EMLA cream was applied to potential venous access sites. Anaesthesia was induced with either thiopentone 5 mg kg^{-1} i.v. or halothane and nitrous oxide in oxygen. Neuromuscular block was produced with atracurium 0.5 mg kg^{-1} and the trachea intubated.

Each child was then allocated randomly to receive one of two possible caudal injections, either 0.25% bupivacaine 0.5 ml kg^{-1} and diamorphine 30 μg kg^{-1}, or 0.25% bupivacaine 0.5 ml kg^{-1} alone. Addition of diamorphine increased the volume of the injectate by 0.03 ml kg^{-1}. The composition of the caudal solution was known only to an anaesthetist who subsequently played no part in the postoperative assessment of the patient. Anaesthesia and normocapnia were maintained by intermittent positive pressure ventilation with halothane and nitrous oxide in oxygen. Intraoperative monitoring included arterial oxygen saturation, ECG, non-invasive arterial pressure monitoring, end-tidal carbon dioxide concentration and nasopharyngeal temperature. Duration of surgery from completion of induction to antagonism of neuromuscular block was recorded for each patient.

After operation, on arrival in recovery, each child received oxygen 4 litre via a face mask and monitoring was continued in the form of pulse oximetry, ECG and non-invasive arterial pressure measurements. Each child was assessed on arrival in recovery, every 15 min for the first hour, at 2 h and then every 2 h for the remainder of the first 24 h. Subsequently, all children were nursed on the same ward and all assessments were carried out by staff nurses unaware of the composition of the injectate given, and trained in the scoring systems used. Monitoring included heart rate, arterial pressure and temperature measurement. Supplementary oxygen was not continued on the ward and arterial oxygen saturation was not assessed.

Each child was prescribed codeine phosphate 1 mg kg^{-1} i.m. and paracetamol 12.5 mg kg^{-1} orally to be given at the discretion of the nursing staff. Additional postoperative observations included

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Table 1 Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). Potential score 4–13[26]

Item	Behaviour	Score
Cry	No cry	1
	Moaning	2
	Crying	2
	Screaming	3
Facial expression	Composed	1
	Grimace	2
	Smiling	0
Verbal	None	1
	Other complaints	1
	Pain complaints	2
	Both complaints	2
	Positive	0
Torso	Neutral	1
	Shifting	2
	Tense	2
	Shivering	2
	Upright	2
	Restrained	2
Touch	Not touching	1
	Reach	2
	Touch	2
	Grab	2
	Restrained	2
Legs	Neutral	1
	Squirming/kicking	2
	Drawn up/tensed	2
	Standing	2
	Restrained	2

Table 2 Sedation score. Potential score 1–4

Item	Score
Awake	1
Drowsy	2
Asleep but rousable	3
Unrousable	4

Table 3 Patient data (mean (SD or range))

Group	Age (months)	Weight (kg)
Diamorphine + bupivacaine (n=22)	31.36 (6–88)	13.34 (4.72)
Bupivacaine alone (n=23)	26.18 (12–57)	12.96 (3.78)

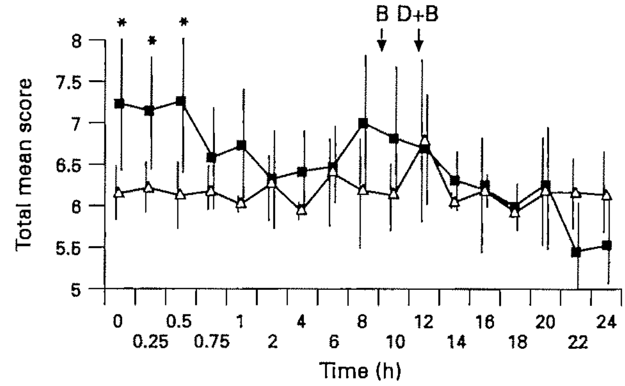

Figure 1 Postoperative pain scores (CHEOPS) for patients receiving either diamorphine and bupivacaine (D + B) (△) or bupivacaine (B) alone (■) (median (95% confidence intervals)). Arrows indicate the median time to first analgesia in the two groups. *$P < 0.05$ (one-way ANOVA).

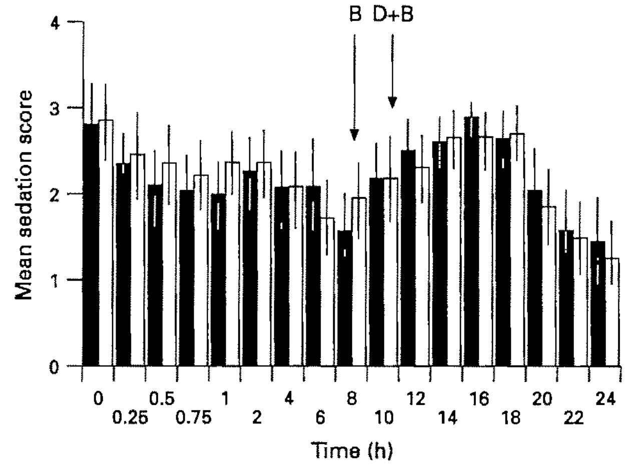

Figure 2 Mean postoperative sedation scores for patients receiving either diamorphine and bupivacaine (D + B) (□) or bupivacaine (B) alone (■) (median (95% confidence intervals)). Arrows indicate the median time to first dose of codeine phosphate in the two groups.

heart rate and non-invasive arterial pressure measurement.

Postoperative assessment comprised scoring for pain and sedation. Ventilatory frequency was also recorded, as were the occurrence of nausea and vomiting, pruritus or urinary retention. The pain score used was the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (table 1). This assigns scores for crying, facial expression, verbal response, touching the wound and torso, and leg position.

The sedation score graded the degree of sedation from awake to unrousable (table 2).

Patient data and duration of operation in each group were compared using the chi-square test. The remaining data, including pain scores, analgesic requirements and incidence of side effects, were analysed using one-way analysis of variance (ANOVA) with Bonferroni's type I error rate correction for multiple tests of significance. Data analysis was performed using SPSS windows version 6.0. $P < 0.05$ was considered statistically significant.

Results

The two groups were similar in age and weight; mean age in the diamorphine group was 31.36 months and in the bupivacaine alone group, 26.18 months (table 3). Mean weights were 13.34 kg and 12.96 kg, respectively.

There was no significant difference between the two groups in mean duration of surgery, which was 90.9 min in the diamorphine group and 80 min in the bupivacaine alone group.

There were no failed blocks in either group. However, there were significant differences in early pain scores with lower scores in the diamorphine group (fig. 1). The difference in scores at times 0, 15 and 30 min were significant ($P < 0.05$). In the bupivacaine alone group, after initially decreasing, pain scores started to increase again after 4–6 h. Median time to first analgesia (either codeine phosphate or paracetamol) in this group was 8.55 h and thereafter pain scores showed a steady decline. In the diamorphine group there was a smaller peak in pain scores

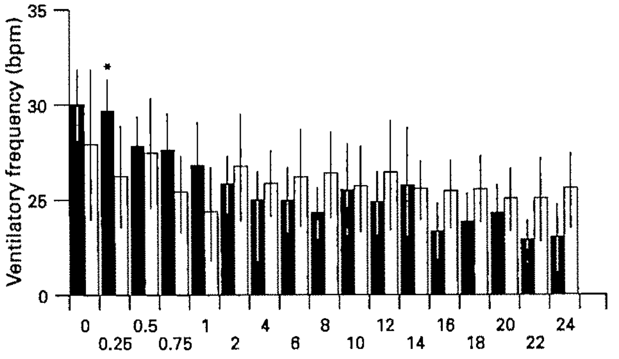

Figure 3 Postoperative ventilatory frequencies for patients receiving either diamorphine and bupivacaine (□) or bupivacaine alone (■) (median (95% confidence intervals)). *$P < 0.05$ (one-way ANOVA).

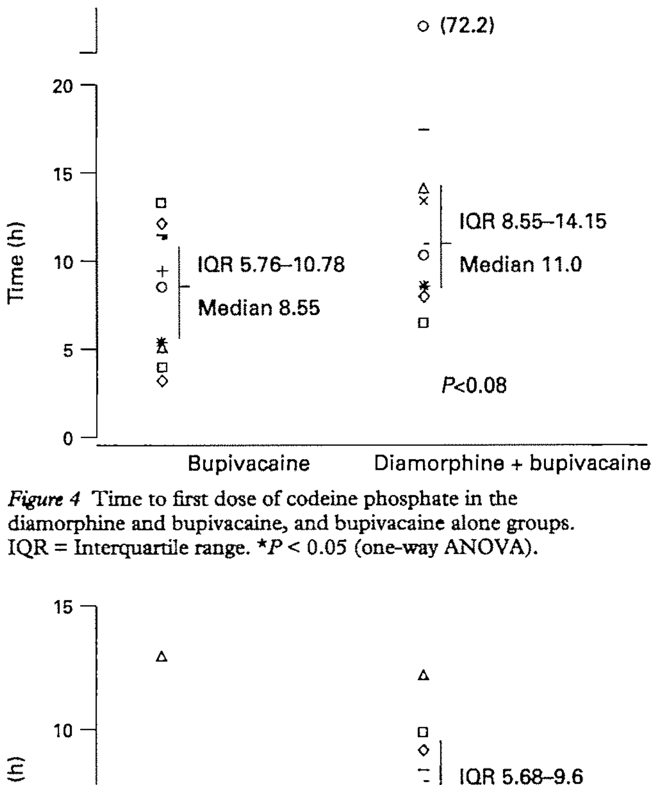

Figure 4 Time to first dose of codeine phosphate in the diamorphine and bupivacaine, and bupivacaine alone groups. IQR = Interquartile range. *$P < 0.05$ (one-way ANOVA).

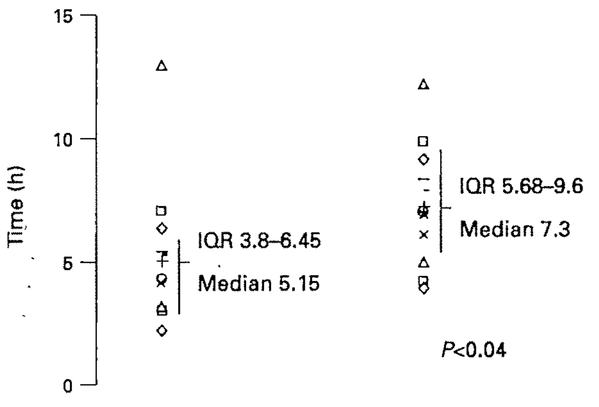

Figure 5 Time to first passage of urine in the diamorphine and bupivacaine, and bupivacaine alone groups. IQR = Interquartile range. *$P < 0.05$ (one-way ANOVA).

at 12 h, the median time to first analgesia was 10.45 h and subsequently pain scores remained relatively constant for the remainder of the first 24 h.

There was no significant difference between the two groups in the degree of sedation, although early scores were slightly higher in the diamorphine group (fig. 2). As may be expected, sedation scores in both groups were high in the immediate postoperative period, then declined during the day, followed by an increase in the evening as the children fell asleep. The first dose of codeine in both groups (median 8.55 h in the bupivacaine alone group and 11 h in the diamorphine group) was associated with an increase in sedation score.

Early postoperative ventilatory frequencies were higher in the bupivacaine alone group, and were significant at 15 min (fig. 3). There were no cases of clinically significant respiratory depression in either group.

Thirteen patients in the diamorphine group and 12 in the bupivacaine alone group did not require codeine phosphate after operation. Of those patients who did, the time to the first dose of codeine was longer in the diamorphine group, although this was not significant (fig. 4). Four patients in the diamorphine group and eight in the bupivacaine alone group received no paracetamol after operation; in those patients who did, the time to first dose was not significantly different between the two groups.

There was an increase in the incidence of nausea and vomiting in the diamorphine group (13.6% compared with 4.3% in the bupivacaine alone group) but this was not significant. There was no incidence of pruritus in either group.

Nine patients in the diamorphine group were electively catheterized during operation for surgical reasons and 10 patients in the bupivacaine alone group. The time to first passage of urine in those patients not catheterized was significantly longer in the diamorphine group, from a median of 5.4 h to 7.6 h after operation ($P < 0.04$) (fig. 5).

Discussion

Caudally administered bupivacaine has long been known to provide good postoperative analgesia with minimal morbidity in children undergoing urogenital surgery.[2–4] More recently, the addition of morphine 50 $\mu g\ kg^{-1}$ to the injected local anaesthetic has been demonstrated to increase the duration and intensity of analgesia without a significant increase in side effects.[5–7] However, at least one of these studies may be criticized in that the volume of bupivacaine given (0.75 $ml\ kg^{-1}$) for orchidopexy may have been inadequate, rendering the local anaesthetic alone group at a disadvantage.[8] Fentanyl 1 $\mu g\ kg^{-1}$ has also been added to caudally administered local anaesthetic but without any improvement in the duration or quality of analgesia after circumcision.[9 10] However, Lejus and colleagues showed that extradural fentanyl 2 $\mu g\ kg^{-1}$ followed by a fentanyl infusion provided a similar level of analgesia as extradural morphine 0.75 $mg\ kg^{-1}$ with a further bolus at 24 h, but as might be expected with a more highly lipid soluble drug, there was a lower incidence of side effects.[11] We could find no study in which diamorphine had been added to caudally administered local anaesthetic in children, although it has been used extensively, and shown to be beneficial in extradural anaesthesia in adults.[12–14]

Diamorphine is 2–3 times as potent and approximately 200 times more lipid soluble than morphine (the olive oil/water partition coefficient of diamorphine is 0.2 compared with 0.016 for morphine)[15] and therefore may cross from the extradural space into the subarachnoid space to bind to spinal opioid receptors much faster than morphine. This results in a more rapid onset of analgesia, usually within 10–15 min compared with 30–60 min with morphine.[16] Consequently, side effects, including rostral spread resulting in late respiratory depression, are less likely.[11,14,17] Because of this increased lipid solubility, diamorphine also diffuses out of the extradural space into surrounding blood vessels faster than morphine, resulting in higher plasma concentrations.[18,19] Inevitably, some of the analgesia and side effects provided by diamorphine may be as a result of systemic absorption rather than a local action on spinal opioid receptors; this leads to a shorter duration of action compared with a relatively non-lipid soluble drug such as morphine. However, it has be shown previously in adults that diamorphine administered extradurally provides a better quality of analgesia than that administered i.m.[14] which implies that the site of action, at least in part, is at the level of the spinal receptor.

The early postoperative pain scores and ventilatory frequency were significantly lower in the diamorphine group. There was no significant difference in the degree of sedation between the two groups, thus the difference in early pain scores could not be attributed solely to increased sedation in the diamorphine group. However, the CHEOPS score is a very sensitive pain assessment tool, whereas sedation score is relatively insensitive, thus it may be that administration of extradural diamorphine, in addition to providing analgesia, led to subtle changes in behaviour resulting in lower pain scores without a comparable increase in sedation score.

Extradural opioids are associated with well recognized side effects, including itching, urinary retention, nausea and vomiting, and respiratory depression, the majority of which may be related to rostral spread.[20] In our study, pruritus did not occur in either group; this may not be surprising as the incidence of pruritus after extradural morphine has been quoted variously as 1–100%.[17,21–23] Nausea and vomiting were more common in the group receiving diamorphine than the bupivacaine alone group, but this was not statistically significant and was low compared with a reported incidence of 50% with extradural morphine.[23] There were no cases of respiratory depression in either group; this may be a reflection of the relatively small size of the study as extradural opioid-induced respiratory depression is comparatively rare with an incidence of 0.2– 0.33% in adult patients receiving extradural morphine.[24,25] In patients receiving extradural diamorphine the incidence is likely to be even lower because of its increased lipid solubility. The time to first passage of urine was significantly longer in those children receiving extradural diamorphine ($P < 0.05$) who were not catheterized during operation, however, no child required intervention with naloxone or catheterization for urinary retention.

In summary, we found that all children in both groups had adequate postoperative analgesia, but the addition of diamorphine $30\ \mu g\ kg^{-1}$ to the caudal injection resulted in a significant reduction in early pain scores. Opioid-induced side effects were few, and only increased time to first passage of urine was statistically significant. We did not encounter any serious side effects such as respiratory depression; this may be related to the small size of the study, the rarity of such complications with extradural opioids and the high lipid solubility of diamorphine.

References

1. Krane EJ. Delayed respiratory depression in a child after caudal epidural morphine. *Anesthesia and Analgesia* 1988; **67**: 79–82.
2. McGown RG. Caudal analgesia in children: 500 cases for procedures below the diaphragm. *Anaesthesia* 1982; **37**: 808–819.
3. Broadman LM. Kiddie caudals: Experience with 1154 consecutive cases without complications. *Anesthesia and Analgesia* 1987; **66**: S191.
4. Kay B. Caudal block for postoperative pain relief in children. *Anaesthesia* 1974; **29**: 610–611.
5. Wolf AR, Hughes D, Hobbs AJ, Prys-Roberts C. Combined morphine–bupivacaine caudals for reconstructive penile surgery in children: systemic absorbtion of morphine and postoperative analgesia. *Anaesthesia and Intensive Care* 1991; **19**: 17–21.
6. Wolf AR, Hughes D, Wade A, Mather SJ, Prys-Roberts C. Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture. *British Journal of Anaesthesia* 1990; **64**: 430–435.
7. Akerman B, Arwestrom E, Post C. Local anesthetics potentiate spinal morphine antinociception. *Anesthesia and Analgesia* 1988; **67**: 943–948.
8. Armitage EN. Regional anaesthesia in children. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia.* Edinburgh: Churchill Livingstone, 1987; 176–183.
9. Jones RDM, Gunawardene WMS, Yeung CK. A comparison of lignocaine 2% with adrenaline 1:200,000 and lignocaine 2% with adrenaline 1:200,000 plus fentanyl as agents for caudal anaesthesia in children undergoing circumcision. *Anaesthesia and Intensive Care* 1990; **18**:194–199.
10. Campbell FA, Yentis SM, Fear DW, Bissonnette MD. Analgesic efficacy and safety of a caudal bupivacaine–fentanyl mixture in children. *Canadian Journal of Anaesthesia* 1992; **39**: 661–664.
11. Lejus C, Roussiere S, Testa S, Ganansia MF, Meignier M, Souron R. Postoperative extradural analgesia in children: comparison of morphine with fentanyl. *British Journal of Anaesthesia* 1994; **72**: 156–159.
12. Enever GR, Noble HA, Kolditz D, Valentine S, Thomas TA. Epidural infusion of diamorphine with bupivacaine in labour: A comparison with fentanyl and bupivacaine. *Anaesthesia* 1991; **46**: 169–173.
13. Bailey CR, Ruggier R, Findley IL. Diamorphine–bupivacaine mixture compared with plain bupivacaine for analgesia. *British Journal of Anaesthesia* 1994; **72**: 58–61.
14. Roulson CJ, Bennett J, Shaw M, Carli F. Effect of extradural diamorphine on analgesia after Caesarean section under subarachnoid block. *British Journal of Anaesthesia* 1993; **71**: 810–813.
15. Stevens LA, Wooton CM. The pharmacokinetic properties of diamorphine. In:Scott B, ed. *Diamorphine its Chemistry, Pharmacology and Clinical Use: 15–45.* Cambridge: Woodhead-Faulkner; 1988.
16. Naulty LS. Intraspinal narcotics. *Clinics in Anesthesiology* 1986; **4**: 145–146.
17. Smith ID, Klubien KE, Wood MLB, Macrae DJ, Carli F. Diamorphine analgesia after caesarean section.Comparison of intramuscular and epidural administration of four dose regimens. *Anaesthesia* 1991; **46**: 970–973.
18. Phillips DM, Moore RA, Bullingham RES, Allen MC, Baldwin D, Fisher A, Lloyd JW, McQuay HJ. Plasma morphine concentrations and clinical effects after thoracic extradural morphine or diamorphine. *British Journal of Anaesthesia* 1984; **56**: 829–835.
19. Watson J, Moore A, McQuay H, Teddy P, Baldwin D, Allen

M, Burlingham R. Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin. *Anesthesia and Analgesia* 1984; **63**: 629.

20. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Nonrespiratory side effects of epidural morphine. *Anesthesia and Analgesia* 1982; **61**: 490–495
21. Reiz S, Westberg M. Side effects of epidural morphine. *Lancet* 1980; **2**: 203.
22. Ballantyne JC, Loach AB, Carr DB. Itching after epidural and spinal opiates. *Pain* 1988; **33**: 149–160.
23. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. *Anesthesia and Analgesia* 1980; **59**: 473–480.
24. Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. *Anesthesiology;* 1991; **75**: 452–465.
25. Gustafsson LL, Schildt B, Jacobsen R. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *British Journal of Anaesthesia* 1982; **54**: 479–485.
26. McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J, Chapman JA. CHEOPS: a behavioral scale for rating post-operative pain in children. *Advances in Pain Research and Therapy* 1985; **9**: 395–402.

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Effect of hypothermia on rectal mucosal perfusion in infants undergoing cardiopulmonary bypass

P. D. BOOKER, D. P. PROSSER AND R. FRANKS

Summary

We have examined the effect of profound hypothermia on gut mucosal perfusion in 20 infants, aged 1.4–45 weeks, requiring cardiopulmonary bypass (CPB). After induction of anaesthesia, a laser Doppler probe was inserted 8 cm into the patient's rectum to allow monitoring of rectal mucosal perfusion ("flux") throughout operation. Steady-state observation periods (5 min with no change in temperature or mean arterial pressure (MAP)) were achieved after 10 min on CPB at 35 °C, after CPB-induced cooling to 15–25 °C, immediately before rewarming and after rewarming to 35 °C. Throughout these periods flow rate was 100 ml kg^{-1} min^{-1}, packed cell volume was kept constant and Pa_{CO_2} maintained at 5.3 ± 0.5 kPa. No vasoactive drugs were used. Initial warm and rewarm MAP values (46 mm Hg) were significantly lower ($P = 0.008$) than during the cold CPB periods (63 and 64 mm Hg). Mean flux in the first cold period (152) was significantly lower ($P = 0.001$) than that in the first warm CPB period (211). Post-rewarm flux (127) was significantly lower than all other CPB flux values ($P = 0.004$). We conclude that although hypothermia significantly reduced mucosal blood flow, rewarming produced even greater reductions in mucosal perfusion that may prove crucial in the development of mucosal hypoxia. (*Br. J. Anaesth.* 1996; **77**: 591–596)

Key words
Heart, cardiopulmonary bypass. Measurement techniques, flowmetry. Gastrointestinal tract, mucosal perfusion. Infants. Hypothermia. Surgery, cardiovascular.

Splanchnic perfusion during cardiopulmonary bypass (CPB) may be jeopardized by vasoconstriction secondary to hypocapnia[1] or to increased concentrations of angiotensin II,[2–5] vasopressin[6] or thromboxane.[7 8] Haemodilution,[9] hypotension[10] and microvessel occlusion, secondary to platelet and leucocyte aggregation,[11] may also reduce oxygen delivery to the gut during CPB. Furthermore, animal[8 12 13] and adult clinical studies[14–17] have confirmed that transient gut mucosal ischaemia may occur during or after CPB. A sufficient reduction in gut mucosal blood flow to induce mucosal hypoxia can cause mucosal barrier breakdown and allow bacterial translocation,[18] as the integrity of the intercellular "tight" junctions is an ATP-dependent process.[19] The incidence of post-CPB gut dysfunction[20 21] and endotoxaemia during CPB[22 23] show a positive correlation with increasing CPB time in adults. Translocation of bacteria and endotoxins from the gut lumen into the portal and systemic circulations is usually self-limiting but may cause sepsis, multiple organ failure (MOF), or both.[24–27]

The incidence of MOF in infants and children undergoing CPB (1.6–3.5%)[28–30] is apparently much higher than that in adults (0.37%).[27 31 32] Although differences in diagnostic criteria or pathophysiology, or both, could account for this disparity, the major dissimilarities between adult and paediatric CPB techniques may be equally important. Profound hypothermia is used in paediatric cardiac surgery to protect vital organs during periods of reduced flow CPB or circulatory arrest. Although the potential for hypothermic CPB to cause gut mucosal hypoxia may be mitigated by the reduction in cellular metabolic rate, hypothermia also increases the affinity of haemoglobin for oxygen and may reduce gut mucosal blood flow.[12 33–35] We studied infants undergoing CPB-induced profound hypothermia and, using laser Doppler flowmetry (LDF), determined how rectal mucosal blood flow changed with temperature, maintaining all other factors constant.

Patients and methods

With local Ethics Committee approval and written, informed parental consent, we studied 20 infants, aged 1.4–45 weeks, requiring profound hypothermia during CPB for elective or urgent cardiac surgery. Infants <2.5 kg in weight or with coarctation of the aorta were excluded. No premedication was used. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and neuromuscular block was produced with vecuronium 0.2 mg kg^{-1} h^{-1}. Anaesthesia was maintained with i.v. infusions of midazolam 240 µg kg^{-1} h^{-1} and diamorphine 24 µg kg^{-1} h^{-1}, supplemented with 0.25% isoflurane in oxygen or air, or both, before CPB.

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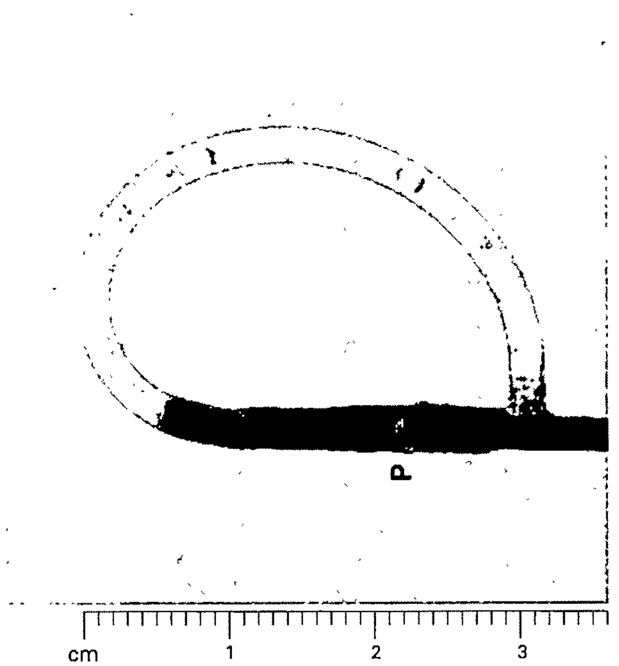

Figure 1 Laser Doppler probe with attached silastic ring. The proximal 10 cm of glass fibre cable had been thickened to provide sufficient rigidity to insert the probe 8 cm into the rectum. The probe's optical prism is located at point P.

A central venous catheter was inserted, a femoral artery cannulated for monitoring of systemic arterial pressure and temperature probes placed in the mid-oesophagus, rectum and nasopharynx. A laser Doppler probe (Moor Instruments Ltd) was inserted 8 cm into the patient's rectum, the probe's special design ensuring that its optical prism lay against the mucosa (fig.1). The probe was connected to a MBF3/D monitor (Moor Instruments Ltd) and computer; later analysis of recordings was made using Moorsoft data interpretation software (Moor Instruments Ltd). The hollow fibre D701 oxygenator (Dideco) used for CPB was primed with a warmed mixture of blood and crystalloid such that the packed cell volume (PCV) 10 min after initiation of CPB was 25 ± 5% and blood and core temperatures 35 ± 0.5°C.

When the patient had been established on non-pulsatile CPB at a flow rate of 100 ml kg^{-1} min^{-1} for 10 min and nasopharyngeal and rectal temperatures were constant at 35 ± 0.5°C, baseline measurements of femoral mean arterial pressure (MAP) and rectal mucosal flux were recorded for another 5 min ("warm-1"). Patients were then cooled on CPB to 15–25°C, depending on the anticipated duration of low flow or circulatory arrest required. The rate of cooling and rewarming was controlled to approximately 1°C min^{-1}. All measurements were repeated during another three "steady-state" 5-min periods: immediately before initiation of low flow ("cold-1"), 10 min after resumption of full flow ("cold-2") and after rewarming to 35°C ("warm-2"). "Steady state" was defined as a period when nasopharyngeal and rectal temperatures did not vary by >0.1°C and MAP did not vary by >2%. Arterial blood-gas tensions, PCV and ionic calcium (Ca^{2+}) concentrations were measured immediately before and after each period. PCV was maintained constant at 25–30 and Ca^{2+} concentration and arterial base deficit were kept within normal limits, although no drugs were given during or within 10 min of any study period. Maintenance of a constant Pa_{O_2} (20 ± 5 kPa) throughout CPB was aided by the use of an in-line Pa_{O_2} monitor (Polystan), and a capnograph (Datex Ltd), attached to the gas outlet port of the oxygenator, helped maintain a constant Pa_{CO_2} (5.3 ± 0.5 kPa, temperature uncorrected, i.e. alpha-stat regulation[36]), together with intermittent arterial blood-gas measurements. All patients maintained MAP at 30–80 mm Hg with a CPB flow rate of 100 ml kg^{-1} min^{-1}, without the use of vasoactive drugs. Inotropic support was given as required to aid weaning from CPB, when the warm-2 readings were complete.

Comparisons between mean flux and mean MAP obtained during the initial warm CPB period and other flux and MAP values were analysed using the Wilcoxon matched pairs signed rank test and exact two-tailed tests (SPSS). Kendall's tau-*b* correlation coefficient was used to examine the relationships between MAP and flux and between CPB time and flux.

Results

Median age of the patients was 16.5 (range 1.4–45) weeks and median weight 5.3 (2.9-7.9) kg (table 1). Patients were cooled to a median nasopharyngeal temperature of 17.9 (14.5–24.6) °C during CPB for periods of 21–132 min. Median CPB time was 122 (102–355) min.

Mean flux values were compared with the mean flux obtained during the first normothermic CPB period (warm-1) (table 2, fig. 2). All CPB data were measured while cardiac output (pump flow rate) was controlled and while the patient was not subject to the effects of vasoactive drugs. Mean cold-1 flux was significantly lower than mean warm-1 flux (P = 0.001). Mean cold-2 flux was not significantly different from mean cold-1 flux (P = 0.12). Mean warm-2 flux was significantly lower than mean warm-1 flux (P = 0.001), mean cold-1 flux (P = 0.004) and cold-2 flux (P = 0.001). Mean flux values before and after CPB were also recorded and compared with mean warm-1 flux, although non-CPB data were obtained during periods when cardiac output was uncontrolled and vasoactive drugs were being used.

MAP increased significantly on cooling (P = 0.001), returning to baseline values on rewarming (table 3, fig. 2). There were no significant differences between MAP during the warm-1 and warm-2 periods (P = 0.91) or between the cold-1 and cold-2 periods (P = 0.98). Table 4 shows the correlations between flux and MAP at different periods. There were no significant correlations between MAP and flux at any time other than at warm-1 (r = 0.33; P = 0.04). Table 5 shows that there were no significant correlations between CPB time and flux.

Discussion

We have demonstrated that rectal mucosal perfusion or "flux", measured using LDF, was reduced significantly secondary to CPB-induced core cooling to

Table 1 Patient data. VSD=Ventricular septal defect, TGA=transposition of the great arteries, TAPVC=total anomalous pulmonary venous connection, AVSD=atrioventricular septal defect, PAB=pulmonary artery band, DILV=double inlet left ventricle, APW=aortic–pulmonary artery window, FALLOT=tetralogy of Fallot, TA=tricuspid atresia

Patient No.	Age (weeks)	Weight (kg)	Diagnosis	Lowest temp. (°C)	Time at lowest temp. (min)
1	41	6.8	TAPVC	16.4	55
2	11	3.8	VSD	16.0	43
3	23	5.7	APW	17.5	51
4	38	7.8	FALLOT	21.2	31
5	16	4.2	AVSD	17.6	34
6	44	6.1	DILV	14.5	132
7	26	5.8	VSD	16.5	51
8	18	4.6	AVSD	15.3	72
9	14	3.9	AVSD	17.9	82
10	13	5.1	AVSD	21.6	60
11	1.3	4.5	TGA	18.3	71
12	45	7.9	TGA, VSD	24.6	29
13	6.8	4.0	TGA	16.6	100
14	8.5	7.3	VSD, PAB	17.9	44
15	16	5.2	AVSD	22.0	21
16	17	5.2	AVSD	19.3	46
17	17	5.4	VSD, AS	21.0	33
18	36	7.3	TA	23.4	37
19	9.0	5.3	VSD	18.5	53
20	1.4	2.9	TGA, VSD	15.9	81
Median (range)	16.5 (1.4–45)	5.3 (2.9–7.9)		17.9 (14.5–24.6)	51 (21–132)

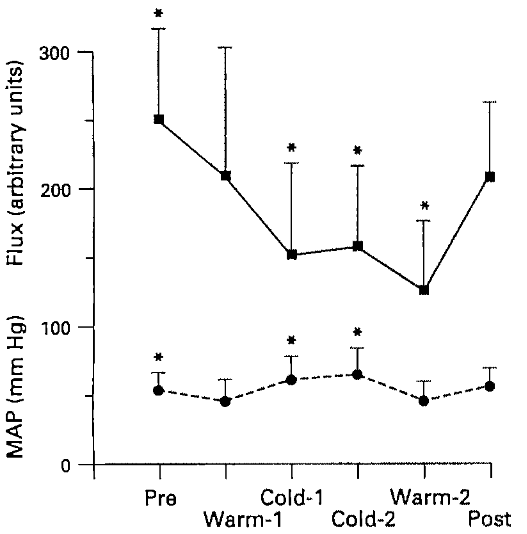

Figure 2 Mean (SD) arterial pressure (MAP) (●) and rectal mucosal flux (■) at each observation period. All readings were obtained over 5 min during steady state conditions. Pre = Before CPB; warm-1 = initial normothermic CPB; cold-1 = before surgery hypothermic CPB; cold-2 = after surgery, hypothermic CPB; warm-2 = at the end of rewarming, normothermic CPB; and post = >20 min after CPB. *Significantly different from values at warm-1 ($P < 0.05$).

Table 2 Mean rectal mucosal flux during each study period (mean (SD)). Values are compared with data obtained during the warm-1 period. Warm-1=Initial normothermic CPB, cold-1=pre-surgery hypothermic CPB, cold-2=post-surgery hypothermic CPB, warm-2=at end of rewarming, normothermic CPB, and post-CPB ≥20 min after CPB

	Flux (arbitrary units)	*P*
Pre-CPB	251 (67)	0.03
Warm-1	211 (93)	—
Cold-1	152 (67)	0.001
Cold-2	159 (59)	0.001
Warm-2	127 (51)	0.001
Post-CPB	209 (55)	0.99

Table 3 Mean femoral arterial pressures during each study period (mean (SD)). Values are compared with data obtained during the warm-1 period. Warm-1=initial normothermic CPB, cold-1=pre-surgery hypothermic CPB, cold-2=post-surgery hypothermic CPB, warm-2=at end of rewarming, normothermic CPB, and post-CPB ≥20 min after CPB

	Arterial pressure (mm Hg)	*P*
Pre-CPB	54.4 (12.9)	0.03
Warm-1	46.2 (15.1)	—
Cold-1	62.5 (14.9)	0.0001
Cold-2	63.7 (21.0)	0.008
Warm-2	45.8 (13.4)	0.91
Post-CPB	55.0 (15.8)	0.06

Table 4 Correlations between MAP and flux at different times. Warm-1=Initial normothermic CPB, cold-1=pre-surgery hypothermic CPB, cold-2=post-surgery hypothermic CPB, warm-2=at end of rewarming, normothermic CPB, and post-CPB ≥20 min after CPB

	r	*P*
Pre-CPB	0.06	0.72
Warm-1	0.33	0.04
Cold-1	0.24	0.14
Cold-2	0.18	0.28
Warm-2	0.07	0.65
Post-CPB	−0.11	0.52

Table 5 Correlations between CPB time and flux at different times. Warm-1=Initial normothermic CPB, cold-1=pre-surgery hypothermic CPB, cold-2=post-surgery hypothermic CPB, warm-2=at end of rewarming, normothermic CPB, and post-CPB ≥20 min after CPB

	r	*P*
Pre-CPB	−0.16	0.33
Warm-1	−0.042	0.80
Cold-1	−0.095	0.56
Cold-2	−0.063	0.70
Warm-2	0.021	0.90
Post-CPB	−0.074	0.65

14–24 °C compared with flux during normothermic CPB at the same flow rate. Further reductions in flux were seen during and after rewarming, although ventricular ejection sometimes produced pulsatile flow during this period. Pulsatile flow would be expected to increase rather than decrease mucosal perfusion,[2 5] compared with non-pulsatile flow which was invariable during the hypothermia period. Furthermore, changes in flux at different temperatures did not correlate with changes in MAP (table 4) and, therefore, reflect variable shunting of blood away from the mucosa.

Experimental animal work[8 13 37] has shown that gut mucosal ischaemia may occur during normothermic CPB despite maintenance of pre-CPB superior mesenteric arterial (SMA) flow rates. Recent animal work has suggested that overall gut blood flow and oxygen consumption may increase progressively during normothermic CPB but are associated with a decrease in mucosal blood flow in the stomach, ileum and rectum.[13] This diversion of blood away from the gut mucosa is thought to be caused by CPB-induced release of vasoactive substances that affect regional blood flow at the macro- or microcirculatory levels, or both.[38] Vasoconstrictors known to be released during CPB in adults include vasopressin,[6] catecholamines,[4 39 40] angiotensin II[2–5] and thromboxane A_2 and B_2.[7 8 41]

Experimental CPB studies using animal models have demonstrated either a reduction,[34] no change[12 35] or an increase[42] in SMA flow during hypothermic (25 °C) CPB. These inconsistent results may be explained by the use of different methodologies, different baseline references and varying perfusion flow rates, and Pa_{CO_2} control. Nevertheless, it would seem from these studies that shunting of blood away from the mucosa is unlikely to be occurring at the arteriolar regulatory level. The decrease in mucosal flux during profound hypothermia, compared with the initial warm CPB value, therefore, must reflect either arteriovenous shunting at the sub-mucosal level or redistribution of blood from the mucosa to the muscularis and serosa. Blood distribution within the gut wall, regulated by pre-capillary sphincter tone, is thought to be governed by local tissue oxygen tension.[43] Thus gut mucosa, which has a high metabolic rate, normally receives 65–92% of total gut blood flow.[44 45] This theory of pre-capillary sphincter regulation, although compatible with the decrease in flux during hypothermia, does not explain the decrease in flux seen during rewarming. We postulate that normal local regulation of pre-capillary sphincter tone was overwhelmed by high concentrations of circulating vasoconstrictors, as demonstrated during normothermic CPB in adults (see above).

Laser Doppler flowmetry (LDF) provides a direct measure of tissue blood flow by using the fact that when laser light is reflected off a moving red blood cell, it undergoes a Doppler frequency shift, the amount of shift being dependent on the speed of the moving object. The laser light is delivered to the tissue surface via a single glass fibre, another fibre being used to collect a portion of the back-scattered light. This photodetector signal is then amplified and the signal-to-noise ratio improved by eliminating noise that is outside the bandwidth of the Doppler frequencies. The analogue signal is then converted into a digital signal for spectral analysis, which is primarily a measure of the average Doppler frequency. The output from a LDF is referred to as "flux", which is a measure of the number of red blood cells flowing through a unit volume of tissue per unit time.

There are problems in using LDF to measure tissue perfusion. First, the technique generates only arbitrary units of measure; however, gut mucosal flux values have been shown experimentally to correlate linearly with changes in gut mucosal blood flow measured using other techniques, over a wide range of flow rates.[46–48] Second, the probe tends to be position-sensitive, although this is not a problem when making successive measurements over a relatively short time period in paralysed patients. Finally, to draw any meaningful conclusions from flux data, it has to be assumed that the tissue measurement volume, at most 6 mm,[3 49] is representative of a larger region of tissue, although fortunately, rectal mucosa has a relatively homogeneous vascular anatomy. Although it cannot be assumed that rectal mucosal blood flow is representative of mucosal blood flow in other areas of the gut, recent animal work has suggested that rectal mucosal perfusion decreases during CPB in a similar manner to that of gastric and ileal mucosa, as measured tonometrically.[13]

Haemodilution results in a reduced density of red blood cells reflecting light back to the monitoring probe, causing a decrease in flux levels with no change in "perfusion". Similarly, a decrease in mean MAP during CPB, compared with levels before CPB, may result theoretically in an increase in mean red cell transit time at the capillary level, further tending to reduce flux values. Thus a reduction in flux during the initial warm CPB period compared with the value before CPB was not unexpected. Thereafter, however, PCV was maintained at a constant level and changes in flux during CPB cannot be attributed to changes in PCV. MAP values changed significantly with temperature, although they did not correlate with flux other than at the initial warm-1 period (table 4, fig. 2). We found no correlation between flux values and duration of CPB (table 5).

Our results contrast with those of Ohri and colleagues, who found no significant difference in jejunal mucosal flux at 28 °C during CPB in dogs compared with baseline readings obtained before CPB.[12] After rewarming, they measured a 70% increase in flux and a simultaneous decrease in jejunal mucosal pH_i from 7.42 to 7.12. These latter results agree with tonometric pH_i data from other experimental and clinical studies in adults and confirm that mucosal hypoxia is most likely to occur during the rewarming phase.[15 50 51] Although a significant correlation between pH_i and blood flow may occur under some conditions,[50 52] pH_i relates to blood flow only insofar as it relates to the adequacy of tissue oxygenation.[53]

Lactate concentrations in skeletal muscle and plasma have been shown, in adult patients during

CPB, to increase after rewarming, suggesting that a shift towards anaerobic cellular metabolism may occur even during normothermic full flow CPB.[54 55] Profound hypothermia and low flow perfusion are likely to exacerbate this tendency. Gut mucosa becomes hypoxic during rewarming not only because of diversion of blood to other parts of the gut but also because of increased oxygen consumption.[12] Increased mucosal oxygen consumption would be expected as the cellular metabolic rate increases with increasing temperature, but hypoxia may also be exacerbated by an oxygen debt being incurred during cooling. CPB-induced hypothermia immediately decreases mucosal oxygen delivery because of decreased blood flow, haemodilution, hypotension and the increased affinity of haemoglobin for oxygen, while tissue cooling and reductions in cellular metabolism occurred more slowly. Although increased tissue requirements for oxygen during rewarming may be met to some extent by increased oxygen extraction,[12 56] experimental work[52] suggests that blood flow is the major factor limiting intestinal oxygen consumption.[52] We have found no evidence that capillary recruitment or precapillary sphincter vasodilatation occurs after rewarming from profound hypothermia, rather the reverse.

In conclusion, our finding of reduced rectal mucosal flux during hypothermia is probably of less clinical relevance than that of decreased flux during and after rewarming, a period when the likelihood of mucosal hypoxia is highest. We recommend that strategies for improving gut perfusion, such as supranormal CPB flow rates or administration of dopexamine[57 58] or epoprostenol,[59] should be directed at the rewarming phase, which represents a particularly critical time for the continued maintenance of normal mucosal barrier function.

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References

1. Fujita Y, Sakai T, Ohsumi A, Takaori M. Effects of hypocapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle. *Anesthesia and Analgesia* 1989; **69**: 152–157.
2. Watkins I, Lucas SK, Gardner TJ, Potter A, Walker WG, Gott VL. Angiotensin II levels during cardiopulmonary byass: a comparison of pulsatile and nonpulsatile flow. *Surgery Forum* 1979; **30**: 229–230.
3. Taylor KM, Bain WH, Morton JJ. The role of angiotensin II in the development of peripheral vasoconstriction during open heart surgery. *American Heart Journal* 1980; **100**: 935–937.
4. Goto M, Kudoh K, Minami S, Nukariya M, Sasaguri S, Watanabe M, Hosoda Y. The renin–angiotensin–aldosterone system and hematologic changes during pulsatile and nonpulsatile cardiopulmonary bypass. *Artificial Organs* 1993; **17**: 318–322.
5. Taylor KM, Bain WH, Russell M, Brannan JJ, Morton JJ. Peripheral vascular resistance and angiotensin II levels during pulsatile and nonpulsatile cardiopulmonary bypass. *Thorax* 1979; **34**: 594–598.
6. Levine FH, Philbin DM, Kono K, Cogins CH, Emerson CW, Austen WG, Buckley MJ. Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass. *Annals of Thoracic Surgery* 1981; **32**: 63–67.
7. Watkins DM, Peterson MB, Kong DL, Kono K, Buckley MJ, Levine FH, Philbin DM. Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow. *Journal of Thoracic and Cardiovascular Surgery* 1982; **84**: 250–256.
8. Cox CS, Zwischenberger JB, Fleming RYD, Alison WE, Myers T, Kurusz M, Herndon DN, Kramer GC. Ileal mucosal hypoperfusion during cardiopulmonary bypass. *Current Surgery* 1992; **49**: 507–510.
9. Crystal GJ, Rooney MW, Salem MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. *Anesthesia and Analgesia* 1988; **67**: 211–218.
10. Lundgren O, Svanvik J. Mucosal haemodynamics in the small intestine of the cat during reduced perfusion pressure. *Acta Physiologica Scandinavica* 1973; **88**: 551–563.
11. Taylor KM. Vasopressor release and multiple organ failure in cardiac surgery. In: Marston A, Bulkley GB, Fiddian-Green RG, eds. *Splanchnic Ischemia and Multiple Organ Failure*. St Louis: Mosby, 1989; 89–99.
12. Ohri SK, Becket J, Brannan J, Keogh BE, Taylor KM. Effects of cardiopulmonary bypass on gut blood flow, oxygen utilization and intramucosal pH. *Annals of Thoracic Surgery* 1994; **57**: 1193–1199.
13. Tao W, Zwischenberger JB, Nguyen TT, Vertrees RA, McDaniel LB, Nutt LK, Herndon DN, Kramer GC. Gut mucosal ischemia during normothermic cardiopulmonary bypass results from blood flow redistribution and increased oxygen demand. *Journal of Thoracic and Cardiovascular Surgery* 1995; **110**: 819–828.
14. Landow L, Phillips DA, Heard SO, Prevost D, Vandersalm TJ, Fink MP. Gastric tonometry and venous oximetry in cardiac surgery patients. *Critical Care Medicine* 1991; **19**: 1226–1233.
15. Ohri SK, Bowles CT, Siddiqui A, Khaghani A, Keogh BE, Wright G, Yacoub MH, Taylor KM. The effect of cardiopulmonary bypass on gastric and colonic mucosal perfusion: a tonometric assessment. *Perfusion* 1994; **9**: 101–108.
16. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Archives of Surgery* 1995; **130**: 423–429.
17. Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin and tumor necrosis factor-alpha concentrations in patients undergoing cardiopulmonary bypass. *Critical Care Medicine* 1993; **21**: 210.
18. Gianotti L, Alexander JW, Fukushima R, Childress CP. Translocation of *Candida albicans* is related to the blood flow of individual intestinal villi. *Circulatory Shock* 1993; **40**: 250.
19. Madara JL. Loosening tight junctions: lessons from the intestine. *Journal of Clinical Investigation* 1989; **83**: 1089–1094.
20. Ohri SK, Desai JB, Gaer JA, Roussak JB, Hashemi M, Smith PL, Taylor KM. Intra-abdominal complications after cardiopulmonary bypass. *Annals of Thoracic Surgery* 1991; **52**: 826–831.
21. Ohri SK, Bjarnason I, Pathi V, Somasundaram S, Bowles CT, Keogh BE, Khaghani A, Menzies IS, Yacoub MH, Taylor KM. Cardiopulmonary bypass impairs small intestinal transport and increases gut permeability. *Annals of Surgery* 1993; **55**: 1080–1086.
22. Rocke DA, Gaffin SL, Wells MT, Keon Y, Brock-Utine JG. Endotoxemia associated with cardiopulmonary bypass. *Journal of the American Medical Association* 1987; **93**: 832–837.
23. Nilsson L, Kulander L, Nystrom S, Eriksson O. Endotoxins in cardiopulmonary bypass. *Journal of the American Medical Association* 1990; **100**: 777–780.
24. Bailey RW, Vickers SM, Porter JM, Meilahn JE, Morris JB, Sussman MS, Buchman TG, Haglund UH, Hamilton SR, Herlong HF. The development of multiple organ system failure in swine following splanchnic ischemia in response to cardiogenic shock. *Gastroenterology* 1989; **96**: A23.
25. Mythen MG, Purdy G, Mackie IJ, McNally T, Webb AR, Machin SJ. Postoperative multiple organ dysfunction syndrome associated with gut mucosal hypoperfusion, increased neutrophil degranulation and C1-esterase inhibitor depletion. *British Journal of Anaesthesia* 1993; **71**: 858–863.

26. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. *Archives of Surgery* 1990; **125**: 403–404.
27. Baue AE. The role of the gut in the development of multiple organ dysfunction in cardiothoracic patients. *Annals of Thoracic Surgery* 1993; **55**: 822–829.
28. Seghaye MC, Duchateau J, Grabitz RG, Faymonville ML, Messmer BJ, Buro RK, von Bernuth G. Complement activation during cardiopulmonary bypass in infants and children: relation to multiple system organ failure. *Journal of Thoracic and Cardiovascular Surgery* 1993; **106**: 978–987.
29. Seghaye MC, Engelhardt W, Grabitz RG, Faymonville ME, Hornchen H, Messmer B- J, von Bernuth G. Multiple system organ failure after open heart surgery in infants and children. *Thoracic and Cardiovascular Surgeon* 1993; **41**: 49–53.
30. Katogi T, Fukuda T, Koyanagi H. Multiple organ failure following open heart surgery in infants and children. *Journal of the Japanese Association of Thoracic Surgery* 1984; **4**: 275–281.
31. Society of Thoracic Surgeons. Data analysis of the Society of Thoracic Surgeons National Cardiac Surgery Database. Chicago: Society of Thoracic Surgeons, 1993.
32. Welling RE, Rath R, Albers JE, Glaser RS. Gastrointestinal complications after cardiac surgery. *Archives of Surgery* 1986; **121**: 1178–1180.
33. Alexander G, Bell AW, Hales JR. Effects of cold exposure on tissue blood flow in the newborn lamb. *Journal of Physiology (London)* 1973; **234**: 65–77.
34. Lazenby WD, Ko W, Zelano JA, Lebowitz N, Shin YT, Isom OW, Krieger KH. Effects of temperature and flow rate on regional blood flow and metabolism during cardiopulmonary bypass. *Annals of Thoracic Surgery* 1992; **53**: 957–964.
35. Mavroudis C, Brown GL, Katzmark SL, Howe WR, Gray LA. Blood flow distribution in infant pigs subjected to surface cooling, deep hypothermia and circulatory arrest. *Journal of Thoracic and Cardiovascular Surgery* 1984; **87**: 665–672.
36. Bove EL, West HL, Pashanik AM. Hypothermic cardiopulmonary bypass: a comparison between alpha and pH stat regulation in the dog. *Journal of Surgical Research* 1987; **42**: 66–73.
37. Tao W, Zwischenberger JB, Nguyen TT, Vertrees RA, Nutt LK, McDaniel LB, Kramer GC. Hypertonic saline dextran for cardiopulmonary bypass reduces gut tissue water but does not improve mucosal perfusion. *Journal of Surgical Research* 1994; **57**: 718–725.
38. Downing SW, Edmunds LHJ. Release of vasoactive substances during cardiopulmonary bypass. *Annals of Thoracic Surgery* 1992; **54**: 1236.
39. Hirvonen J, Huttunen P, Nuutinen L, Pekkarinen A. Catecholamines and free fatty acids in plasma of patients undergoing cardiac operations with hypothermia and bypass. *Journal of Clinical Pathology* 1978; **31**: 949.
40. Reed HL, Chernow B, Lake CR, Zaloga GP, Stoiko MA, Beardsly D, Cruess D, Lee C, Smallridge RC. Alterations in sympathetic nervous system activity with intraoperative hypothermia during coronary artery bypass surgery. *Chest* 1989; **95**: 616–622.
41. Davies GC, Sobel M, Salzman EW. Elevated plasma fibrinopeptide A and thromboxane B levels during cardiopulmonary bypass. *Circulation* 1980; **61**: 808.
42. Utley JR, Wachtel C, Cain RB, Spaw EA, Collins JL, Stephens DB. Effects of hypothermia, hemodilution and pump oxygenation on organ water content, blood flow and oxygen delivery and renal function. *Annals of Thoracic Surgery* 1981; **31**: 121–133.
43. Granger HJ, Nyhof RA. Dynamics of intestinal oxygenation: interactions between oxygen supply and uptake. *American Journal of Physiology* 1982; **243**: G91–G96.
44. Chou CC, Grassmick B. Motility and blood flow distribution within the wall of the gastrointestinal tract. *American Journal of Physiology* 1978; **235**: H34–H39.
45. Fan F, Schuesller GB, Chen RYZ, Chien S. Determinations of blood flow and shunting of 9–u and 15–um spheres in regional beds. *American Journal of Physiology* 1979; **237**: H25–H33.
46. DiResta GR, Kiel JW, Riedel GL, Kaplan P, Shepherd AP. Hybrid blood flow probe for simultaneous H2 clearance and laser-Doppler velocimetry. *American Journal of Physiology* 1987; **252**: G573–G581.
47. Larson MV, Ahlquist DA, Karlstrom L, Sarr MG. Intraluminal measurement of enteric mucosal perfusion: relationship to superior mesenteric artery flow during basal and postprandial states in the dog. *Surgery* 1994; **115**: 118–126.
48. Ahn H, Lindhagen J, Nilsson GE, Salerud GE, Jodal M, Lundgren O. Evaluation of laser Doppler flowmetry in the assessment of intestinal blood flow in cat. *Gastroenterology* 1985; **88**: 951–957.
49. Johansson K, Ahn H, Lindhagen J, Lundgren O. Tissue penetration and measuring depth of laser Doppler flowmetry in the gastrointestinal application. *Scandinavian Journal of Gastroenterology* 1987; **2**: 1081–1088.
50. Poole JW, Sammartano RJ, Boley SJ. The use of tonometry in the early diagnosis of acute mesenteric ischemia. *Current Surgery* 1987; **44**: 21–24.
51. Fiddian-Green RG. Gut mucosal ischemia during cardiac surgery. *Seminars in Thoracic and Cardiovascular Surgery* 1990; **2**: 389–399.
52. Grum CM, Fiddian-Green RG, Pittenger GL, Grant JB, Pothman D, Dantzker DR. Adequacy of tissue oxygenation in intact dog intestine. *Journal of Applied Physiology* 1984; **56**: 1065–1069.
53. Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *British Journal of Anaesthesia* 1995; **74**: 591–606.
54. Del Canale S, Vezzani A, Belli L, Coffrini E, Guariglia A, Ronda N, Vitali P, Beghi C, Fesani F, Borghetti A, Fiaccadori E. Comparative clinical study on the effects of cardiopulmonary bypass with different flows and pressures on skeletal muscle cell metabolism in patients undergoing coronary bypass grafting. *Journal of Thoracic and Cardiovascular Surgery* 1990; **99**: 327–334.
55. Landow L. Splanchnic lactate production in cardiac surgery patients. *Critical Care Medicine* 1993; **21**: S84–S91.
56. Granger HJ, Norris CP. Intrinsic regulation of intestinal oxygenation in the anesthetized dog. *American Journal of Physiology* 1980; **238**: H836–H843.
57. Smithies MN, Yee TH, Jackson L, Beale R, Bihari D. Protecting the gut and the liver in the critically ill: effects of dopexamine. *Critical Care Medicine* 1994; **22**: 789–795.
58. Trinder TJ, Lavery GG, Fee JP, Lowry KG. Correction of splanchnic oxygen deficit in the intensive care unit: dopexamine and colloid versus placebo. *Anaesthesia and Intensive Care* 1995; **23**: 178–182.
59. Wu Y, Li SS, Campbell KA, Sitzmann JV. Modulation of splanchnic vascular sensitivity to angiotensin II. *Surgery* 1991; **110**: 162–168.

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Gut mucosal perfusion in neonates undergoing cardiopulmonary bypass

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Summary

We studied gut mucosal perfusion in 24 neonates requiring cardiopulmonary bypass (CPB). Group A patients (n = 12) had obstruction to their aorta such that gut perfusion before operation was dependent on flow through a ductus arteriosus (DA). Group B neonates were of similar age and size and required a similar duration of CPB, but did not have a DA. An orogastric tonometer allowed intermittent calculations of gastric intramucosal pH (pH_i), and rectal mucosal perfusion ("flux") was monitored using laser Doppler flowmetry. Measurements of arterial base deficit, and lactate and pyruvate concentrations were made intermittently. Before CPB, mean femoral arterial pressure (MAP) and base deficit in group A were not significantly different from those in group B. However, mean flux before CPB was significantly lower and the lactate/pyruvate (L/P) ratio was significantly higher in group A compared with group B. Mean pH_i was below normal (<7.26) throughout the operative period in group A, although it remained normal (>7.33) in group B. After corrective surgery, both during warm CPB and after CPB, we found no significant difference in MAP, L/P ratio or base deficit between the groups, but both flux and pH_i were significantly lower in group A compared with group B. We conclude that neonates requiring aortic arch surgery may be at particular risk of gut mucosal hypoxia both before and after operation. (*Br. J. Anaesth.* 1996; **77**: 597–602)

Key words
Measurement techniques, flowmetry. Measurement techniques, tonometry. Gastrointestinal tract, mucosal perfusion. Neonate. Heart, cardiopulmonary bypass. Surgery, cardiovascular.

Splanchnic perfusion during cardiopulmonary bypass (CPB) may be jeopardized by vasoconstriction secondary to hypocapnia[1] or to increased concentrations of angiotensin II,[2] vasopressin,[3] thromboxane,[4] endothelin-1[5] and catecholamines.[3 6] Haemodilution,[7] hypotension[8] and microvessel occlusion secondary to platelet, leucocyte or erythrocyte aggregation,[9] may also reduce oxygen delivery to the gut during CPB. Animal[10 11] and adult[12 13] studies have confirmed that transient gut mucosal ischaemia may occur during and after CPB. A sufficient reduction in gut mucosal blood flow to induce mucosal hypoxia can cause mucosal barrier breakdown and allow bacterial translocation,[14] as the integrity of the intercellular "tight" junctions is an ATP-dependent process.[15] Translocation of bacteria and endotoxins from the gut lumen into the portal and systemic circulations is usually self-limiting but may cause sepsis or multiple organ failure, or both.[16] However, bacterial and endotoxin translocation may not be necessary for distant organ injury after gut ischaemia–reperfusion.[17] The reperfused gut may cause oxidant-induced mast cell activation and priming of circulating neutrophils, resulting in pulmonary injury secondary to neutrophil sequestration.[18]

We postulated that neonates with coarctation, or other aortic arch anomalies affecting descending aortic blood flow, may be at particular risk of developing splanchnic ischaemia in the perioperative period. We have compared gut mucosal perfusion in neonates with ductus arteriosus (DA)-dependent circulations with a control group with normal aortic arch anatomy; patients were of a similar mean age and weight, and CPB times were comparable. We used a tonometric technique to assess gastric mucosal perfusion[19] and laser Doppler flowmetry to monitor rectal mucosal perfusion.[20]

Patients and methods

With local Ethics Committee approval and written, informed parental consent, we studied 12 neonates, > 2.0 kg in weight, aged 3–15 days, requiring CPB for repair of an cardiac anomaly, together with either a coarctation or interrupted aortic arch. Another 12 neonates with normal aortic arch anatomy (with no DA), requiring CPB for cardiac surgery, were also studied (table 1). Patients requiring preoperative vasoactive drugs, other than prostaglandins, were excluded. None of the neonates had significant fetal distress *in utero*. There was no significant difference between mean age, weight or CPB times in the two groups of patients, but mean aortic clamp time in the

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Table 1 Individual patient data. CPB = Cardiopulmonary bypass, AC = aortic clamp, IAA = interrupted aortic arch, ASD = atrial septal defect, VSD = ventricular septal defect, HLHS = hypoplastic left heart syndrome, TGA = transposition of the great arteries, TAPVC = total anomalous pulmonary venous connection

Patient No.	Diagnosis (days)	Age (kg)	Weight (min)	CPB time (min)	AC time
1	IAA, ASD	12	2.7	228	68
2	IAA, VSD	10	3.5	153	51
3	IAA, VSD	12	3.5	92	39
4	HLHS	4	3.1	150	83
5	HLHS	15	4.0	135	62
6	HLHS	3	3.4	420	60
7	IAA, ASD	9	3.5	130	70
8	IAA, VSD	7	3.5	141	61
9	IAA, ASD	8	3.0	107	55
10	IAA, VSD	11	2.5	169	86
11	IAA, VSD	7	3.4	158	51
12	IAA, VSD	6	3.3	143	58
13	TGA	11	4.5	130	68
14	TGA, VSD	43	4.0	190	112
15	TGA, VSD	10	2.9	360	81
16	TGA	24	3.2	144	77
17	TGA	5	4.5	275	70
18	TGA	57	3.5	120	72
19	TAPVC	11	2.6	98	48
20	TGA	8	2.4	356	76
21	TGA	10	5.5	135	73
22	TGA	17	3.4	230	93
23	TGA	5	3.9	232	85
24	TGA	4	2.2	150	72

Table 2 Age, weight, oxygen saturation (sat.) before cardiopulmonary bypass (pre-CPB), and CPB and aortic clamp (AC) times in the two groups patients (mean (SD or range)

	Group A	Group B	*P*
Age (days)	8.7 (3–15)	17.1 (4–57)	0.28
Weight (kg)	3.3 (0.4)	3.4 (0.8)	0.85
Pre-CPB oxygen sat. (%)	88.8 (3.0)	81.5 (3.5)	0.001
CPB time (min)	169 (86)	202 (90)	0.42
AC time (min)	62 (13)	77 (15)	0.01

control group B was significantly longer than in group A (table 2).

No premedication was used. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and neuromuscular block was produced with vecuronium 0.2 mg kg^{-1}·h^{-1}. Anaesthesia was maintained with i.v. infusions of midazolam 240 μg kg^{-1} h^{-1} and diamorphine 24 μg kg^{-1} h^{-1}, supplemented with 0.25% isoflurane in oxygen or air, or both, before CPB. A central venous catheter was inserted and a femoral artery cannulated for monitoring of systemic arterial pressure. A urinary catheter and nasopharyngeal and oesophageal temperature probes were inserted and a peripheral tissue oxygen saturation probe was taped in place.

A laser Doppler probe (Moor Instruments Ltd) was inserted 7 cm into the patient's rectum, the probe's special design ensuring that its optical prism lay against the mucosa.[20] The probe was connected to a MBF3/D monitor (Moor Instruments Ltd) and computer; later analysis of recordings was made using Moorsoft data interpretation software (Moor Instruments Ltd). A Trip sigmoid tonometer (Tonometrics, Inc., MA, USA) was inserted orally into the patient's stomach. Correct positioning of the tonometer was aided by the sight of a small bulging of the anterior abdominal wall as it was gently advanced, later confirmed by chest x-ray obtained after operation. Saline 0.9% (2.5 ml) was then introduced anaerobically into the tonometer balloon.

After the chest was opened, but before surgical manipulation of the great vessels, baseline recordings of rectal mucosal flux and femoral mean arterial pressure (MAP) were made over a 5-min period. A sample of arterial blood was obtained for measurement of Pa_{O_2}, Pa_{CO_2}, PCV and base deficit. Ionic calcium (Ca^{2+}), bicarbonate, lactate and pyruvate concentrations were measured and, subsequently, the lactate/pyruvate (L/P) ratio was calculated. $P\text{CO}_2$ of the saline in the tonometer balloon was determined using a Ciba-Corning 865 analyser. Gastric intramucosal pH (pH_i) was calculated using the Henderson–Hasselbalch equation and time correction factors as supplied by Tonometrics, Inc. The inspired oxygen concentration before CPB was adjusted such that peripheral oxygen saturation was 75–90% in all patients, although group A patients had a significantly higher mean saturation than group B patients (see table 2).

The hollow fibre D701 oxygenator (Dideco) used for CPB was primed with warmed blood and crystalloid such that blood and core temperatures 10 min after initiation of CPB were 34 ± 0.5 °C and PCV was 25 ± 5%. When the patient had been established on non-pulsatile CPB at a flow rate of 100 ml kg^{-1} min^{-1} for 10 min and nasopharyngeal temperature varied by <0.1 °C min^{-1}, another arterial blood sample was obtained for measurements of PCV, base deficit and bicarbonate, lactate and pyruvate concentrations. MAP and rectal mucosal flux were recorded for another 5 min before the patient was cooled during CPB to 15–25 °C, depending on the anticipated duration of low flow or circulatory arrest required. The rate of cooling and rewarming was controlled to approximately 1 °C min^{-1}. Throughout CPB, PCV was maintained at 25 ± 5% and Ca^{2+} concentration and base deficit were kept within normal limits, although no drugs were given within 15 min of any study period. Intermittent arterial blood-gas measurement was used to maintain a constant Pa_{O_2} (20 ± 5 kPa) throughout CPB, aided by the use of an in-line Pa_{O_2} monitor (Polystan). Similarly, a capnograph (Datex Ltd), attached to the gas outlet port of the oxygenator helped maintain a constant Pa_{CO_2} (5.3 ± 0.5 kPa, temperature uncorrected, i.e. alpha-stat regulation).[21] No vasoactive drugs were required in any patient to maintain MAP at 30–80 mm Hg during warm CPB using a flow rate of 100 ml kg^{-1} min^{-1}. When the patient was rewarmed on CPB and stabilized at 35 ± 0.1 °C for 5 min, another set of blood and tonometer samples, flux and haemodynamic readings were obtained over another 5 min. Inotropic support was given as required to aid weaning from CPB when the rewarm readings were complete. A final set of readings and blood samples were obtained just before transfer to the ICU, usually about 1 h after CPB.

Comparisons between mean flux, mean pH, mean MAP, mean base deficit and mean L/P ratio obtained at each period in the two groups were

Table 3 Mean arterial pressure (MAP), gastric pHi, lactate/pyruvate (L/P) ratio, rectal mucosal flux and arterial base deficit (BD) in the two groups before corrective surgery

	Pre-CPB			Warm CPB-1		
	Group A (n=12)	Group B (n=12)	P	Group A (n=6)	Group B (n=8)	P
MAP	42 (5.8)	43 (7.5)	0.80	46 (20)	38 (7.8)	0.44
pH_i	7.25 (0.12)	7.34 (0.08)	0.07	7.23 (0.04)	7.41 (0.04)	0.10
L/P ratio	16.8 (5.5)	11.4 (5.5)	0.05	27.1 (6.6)	20.8 (10.6)	0.43
Flux	154 (101)	275 (147)	0.03	158 (102)	236 (175)	0.61
BD	3.8 (5.4)	2.5 (5.4)	0.92	0.3 (3.5)	0.0 (3.3)	0.90

Table 4 Mean arterial pressure (MAP), gastric pH_i, lactate/pyruvate (L/P) ratio, rectal mucosal flux and arterial base deficit (BD) in the two groups after corrective surgery. Two patients in group A and one patient in group B did not survive after cardiopulmonary bypass (CPB). All patients were receiving enoximone and either dobutamine or adrenaline after CPB

	Warm CPB-2			Post-CPB		
	Group A (n=12)	Group B (n=12)	P	Group A (n=6)	Group B (n=8)	P
MAP	44 (16.3)	45 (12.0)	0.92	52 (8.2)	45 (8.2)	0.13
pH_i	7.21 (0.18)	7.37 (0.05)	0.04	7.07 (0.24)	7.36 (0.08)	0.0004
L/P ratio	33.5 (10.8)	35.3 (19.5)	0.75	37.0 (19.3)	27.0 (19.2)	0.15
Flux	106 (63)	183 (68)	0.01	179 (85)	276 (115)	0.04
BD	4.2 (3.9)	3.3 (4.1)	0.58	6.5 (7.1)	1.6 (3.2)	0.10

Table 5 Inotrope requirements in the two groups of patients after successful weaning from cardiopulmonary bypass (CPB). All patients received enoximone (EN) 10 μg kg^{-1} min^{-1}. The two patients in group A and one patient in group B who did not survive 1 h after CPB are excluded. All other patients received *either* adrenaline (AD) *or* dobutamine (DB). Mean "combined" dose assumes AD 1 μg kg^{-1} min^{-1} = DB 20 μg kg^{-1} min^{-1}

Inotrope	Group A (n=10)	Group B (n=11)	P
No. of patients requiring AD	4	3	0.90
Mean dose of AD (μg kg^{-1} min^{-1})	2.5 (1.7)	2.3 (1.5)	0.97
No. of patients requiring DB	6	8	0.63
Mean dose of DB (μg kg^{-1} min^{-1})	11.7 (2.6)	13.1 (5.3)	0.69
Mean "combined" dose (μg kg^{-1} min^{-1})	27.0 (28.2)	22.3 (21.3)	0.87

analysed using the Wilcoxon test and SPSS exact test (SPSS UK Ltd). Kendall's tau-*b* rank correlation coefficient was used to assess associations between MAP, base deficit, flux, pH_i and L/P ratios at every period.

Results

Mean flux before CPB in group A (154) was significantly lower than that in group B (275) (P = 0.03) (table 3, fig. 1). Although mean pH_i before CPB in group A (7.25) was lower than that in group B (7.34), this difference was not statistically significant. Mean L/P ratio before CPB was significantly higher in group A (16.8) than that in group B (11.4) (P = 0.05), although there were no statistically significant differences between the groups in MAP or base deficit before CPB.

Mean flux (158) and mean pH_i (7.23) in group A were lower than the mean values in group B (236 and 7.41, respectively) during the initial warm CPB period before corrective surgery. However, these differences were not significant, probably because it was not possible in every patient to obtain warm, stable temperatures during CPB for at least 30 min before commencement of core cooling. There were no significant differences between the two groups in mean L/P ratios, MAP or base deficit measured after rewarming on CPB after corrective surgery (table 4). However, mean flux in group B (183) was significantly higher (P = 0.01) than that in group A (106) at this time. In addition, mean gastric pH_i in group A (7.21) was significantly lower (P = 0.04) than that in group B, which remained normal (7.37).

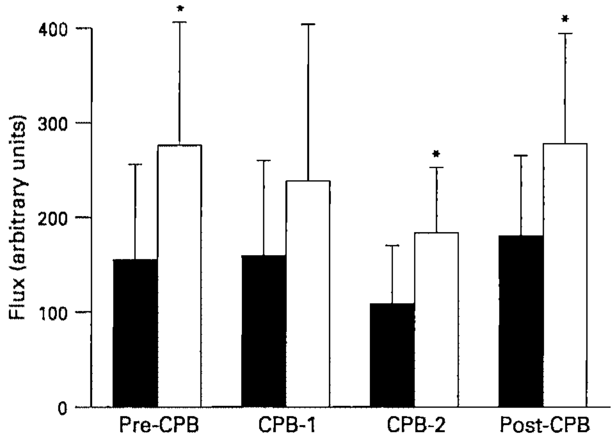

Figure 1 Mean (SD) rectal mucosal perfusion ("flux") in the two groups of patients at each observation period. CPB= Cardiopulmonary bypass. CPB-1 = warm CPB before corrective surgery; CPB-2 = warm CPB after corrective surgery. Group A (■) patients had aortic arch obstruction with ductus-dependent circulations; group B (□) patients had normal aortic arch anatomy. *P < 0.05.

Table 6 Significant correlations between arterial base deficit (BD), gastric pH_i, and lactate/pyruvate (L/P) ratios (all patients). There were no other significant correlations between any other measured variables. r = correlation coefficient, P = level of significance. CPB= Cardiopulmonary bypass; Warm CPB-2 = after corrective surgery but still requiring CPB

	Pre-CPB BD	Warm CPB-2 BD	Post-CPB BD	Post-CPB pH_i
Pre-CPB pH_i	r=−0.33 P=0.04			
Warm CPB-2 pH_i		r=−0.39 P=0.03		
Warm CPB-2 L/P		r=0.41 P=0.02		
Post-CPB L/P			r=0.37 P=0.03	r=−0.43 P=0.02
Post-CPB BD				r=−0.49 P=0.004

Two patients in group A and one patient in group B did not survive after CPB. To enable successful weaning from CPB, all patients received enoximone 10 μg kg^{-1} min^{-1} and either dobutamine or adrenaline; we found no significant differences between the two groups in the mean dose of dobutamine or adrenaline required (table 5). In addition, for the purposes of statistical comparison and on the basis of data from an ongoing study, we assumed adrenaline 1 μg kg^{-1} min^{-1} produced an inotropic effect equivalent to dobutamine 20 μg kg^{-1} min^{-1}. There was no significant difference between the "combined" inotrope requirements in the two groups. Mean pH_i in group A (7.07) was significantly lower than that in group B (7.36) after CPB (P = 0.0004) (table 4). Mean flux in group A patients, although slightly higher than the mean pre-CPB value, remained significantly lower than that in group B (P = 0.04). There were no significant differences in mean L/P ratios, MAP or base deficit between the two groups after CPB.

Gastric pH_i showed a significant correlation with base deficit both before and after CPB and with L/P ratios after CPB. Significant correlations between arterial base deficit and L/P ratios were found both at warm CPB after corrective surgery and after CPB (table 6, fig. 2).

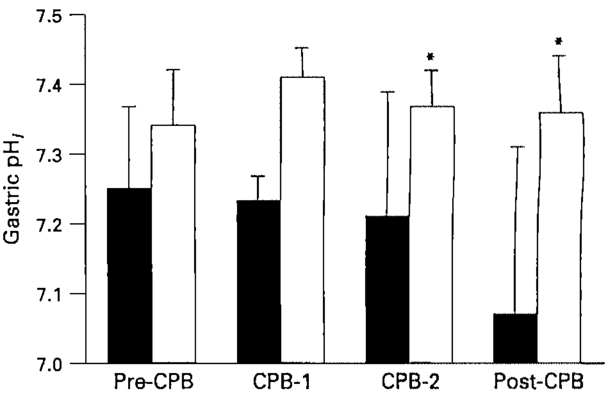

Figure 2 Mean (SD) gastric pH_i in the two groups of patients at each observation period. CPB = Cardiopulmonary bypass. CPB-1 = warm CPB before corrective surgery; CPB-2 = warm CPB after corrective surgery. Group A (■) patients had aortic arch obstruction with ductus-dependent circulations; group B (□) patients had normal aortic arch anatomy. $^*P < 0.05$.

Discussion

We have shown that neonates with aortic arch anomalies (group A) may have periods of gut mucosal ischaemia not only before, but also shortly after corrective surgery. Mean gastric intramucosal pH (pH_i) was <7.26 in group A patients, before, during and after surgery, whereas pH_i remained >7.33 throughout the operative period in our control group B patients with normal aortic arch anatomy. We believe, on the basis of these results, other neonatal data we have collected (unpublished) and adult studies[13 22] that a pH_i value <7.33 is below normal and indicates mucosal hypoxia. In addition, rectal mucosal perfusion ("flux") was significantly lower in group A than that in group B both before and after corrective surgery. The significant difference in gastric pH_i and rectal mucosal flux between the two groups of neonates after surgery suggests that despite anatomical correction of the aortic obstruction and a resulting increase in total blood flow to the gut, early post-surgical mucosal perfusion in group A patients remained below normal.

The requirement for saline to be introduced into the tonometer balloon for at least 30 min before sampling implied that the number of observations was reduced during the initial warm CPB (before surgery) period (table 3). Statistical analysis of this comparative data may therefore underestimate the real difference between the two groups at this time. Measurement of tonometer saline $P\text{CO}_2$ during the other periods was after an equilibration time of >45 min, to allow accurate calculation of pH_i. The potential problems and assumptions that underlie the use of laser Doppler flowmetry (LDF) to measure rectal mucosal blood flow have been reported previously.[20]

Notwithstanding evidence that prostaglandin E_1, administered before CPB only to group A patients, may increase gut mucosal blood flow,[23] ultrasound studies of neonatal mesenteric arterial flow have indicated that the presence of a ductus arteriosus (DA) may lead to compromised splanchnic perfusion.[24 25] Although necrotizing enterocolitis has been reported as a complication of hypoplastic aortic arch,[26] we are not aware of any previous studies that have examined the relationship between DA-dependent perfusion, which is peculiar to this age group, and gut ischaemia. Nevertheless, the preoperative difference in both mucosal pH_i and flux between our two groups of patients was not unexpected.

We have confirmed our previous finding that rectal mucosal flux is decreased after rewarming following CPB-induced hypothermia.[20] In group B patients, with normal aortic arch anatomy, flux during CPB after rewarming was significantly lower than flux before CPB ($P = 0.01$). However, the reduction in mucosal perfusion did not result in an abnormal gastric pH_i in this group of patients, suggesting that although mucosal blood flow had been reduced, it had not decreased sufficiently to cause mucosal hypoxia. In contrast, rewarm flux in group A was not only significantly lower than that in group B, but was associated with gastric intramucosal acidosis. These data are compatible with the premise that when mucosal blood flow decreases to below the critical level required to maintain mucosal cell homeostasis, pH_i decreases to below normal values, indicating mucosal hypoxia. One hour after weaning from CPB, pH_i in group A decreased to 7.07, despite a small increase in rectal mucosal flux, confirming data from an adult study which showed that pH_i values after CPB do not necessarily correlate with global splanchnic perfusion.[27] Nevertheless, the flux value of 179 after CPB in group A patients compares with our "normal" flux values of 250–300 (values taken from this study, previous published work[20] and other unpublished data). This finding suggests that although gut mucosal blood flow had improved (by about 16%) after surgery, this increase had not been sufficient to return values to "normal".

CPB-induced impairment of macro- or microcirculatory vasoregulation, or both, has been suggested as a cause of heterogeneous distribution of gut blood flow after CPB,[27] although our data for group B patients do not support this. The relatively low flux after CPB in group A patients may have been a result of local vascular endothelial release of the potent long-lasting vasoconstrictor endothelin-1, which is known to increase in response to hypoxia or reduction in regional perfusion pressure.[28 29] Alternatively, the more severe gut mucosal ischaemia–reperfusion injury experienced by group A compared with group B patients may have caused an increase in local nitric oxide inhibition[18] or eicosanoid release.[4 18] In addition, there is evidence that reperfusion injury can cause severe disruption of the mucosal microcirculation. Boros, Takaichi and Hatanaka[9] have shown, in an animal model, that reperfusion of ischaemic gut mucosa can lead to capillary block caused by erythrocyte plugging, possibly secondary to perivascular oedema and capillary compression.

In addition to below-normal mucosal blood flow, another possible cause of mucosal hypoxia after CPB is that of increased cellular oxygen consumption secondary to reperfusion injury[30] or use of inotropic drugs.[31] Our two groups of patients required equipotent amounts of inotropic support (table 5). Data from an ongoing study (unpublished) suggests that adrenaline, given in a dose of $>1\ \mu g\ kg^{-1}\ min^{-1}$, produces a higher mean systemic vascular resistance than dobutamine when given in an equipotent inotropic dose. We therefore compared the dose rates of adrenaline and dobutamine separately in the two groups of patients, but found no significant difference. It would seem, therefore, that the vasoconstrictor effect of high-dose adrenaline, although unquantified in this study, was unlikely to have been the main determinant of mucosal hypoxia after CPB in group A patients. However, these data do not preclude the possibility that an increase in local endothelin-1 concentrations in group A patients would have potentiated the splanchnic vasoconstrictor effects of high-dose adrenaline.[32]

Base deficit[33] and L/P ratios[34] are thought to be useful global indices of cellular oxygenation. L/P values >10 are indicative of tissue hypoxia; the higher the value, the greater the magnitude of the oxygen debt. Although lactate generation *per se* does not cause acidaemia, increased lactate production as a result of development of anaerobic metabolism is associated with degradation of high-energy phosphates, leading to increased production of hydrogen ions and carbon dioxide. Reperfusion of ischaemic tissue would be expected therefore to wash out both accumulated lactate and hydrogen ions, causing an increase in both L/P ratio and base deficit. Although the preoperative L/P ratio in group A was significantly higher than that in group B, hyperlactataemia in the former group was not associated with significant acidaemia. This suggests that, despite better peripheral tissue oxygen saturation than group B, tissue hypoxia in group A was occurring, although it was not severe or extensive. Hypothermic CPB may decrease both hepatic lactate clearance and pyruvate metabolism such that the L/P ratio remains unchanged.[34 35] However, in all of our patients, L/P ratios increased and remained abnormally high during CPB, probably because of the lactate and citrate load associated with a blood prime, and lactate washout with reperfusion after periods of low flow. An imbalance between regional oxygen delivery and tissue oxygen consumption during rewarming causes hyperlactataemia and our finding of similar high L/P values after CPB in both groups of patients suggests that hypoxia in tissues other than the gut may occur in all neonates after CPB. We found significant correlations between base deficit and L/P ratios after surgery and between pH_i and base deficit before and after surgery. However, the non-specific indices of tissue hypoxia, L/P ratio and base deficit, were generally unhelpful in identifying those patients most at risk of gut mucosal hypoxia.

We have shown that neonates requiring aortic arch surgery are at risk of below-normal gut mucosal perfusion and hypoxia, not only before and during corrective surgery, but also after operation, despite resultant normal aortic arch perfusion. Although gastric and rectal mucosal perfusion cannot necessarily be related to ileal or colonic perfusion, we believe that further studies are required to determine if strategies that may improve gut perfusion, such as administration of dopexamine, prevent or ameliorate the gut mucosal hypoxia we have observed in neonates with aortic arch anomalies.

Acknowledgement

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References

1. Fujita Y, Sakai T, Ohsumi A, Takaori M. Effects of hypocapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle. *Anesthesia and Analgesia* 1989; **69**: 152–157.
2. Reilly PM, Bulkley GB. Vasoactive mediators and splanchnic perfusion. *Critical Care Medicine* 1993; **21**: S55–S68.
3. Lehot JJ, Villard J, Piriz H, Philbin DM, Carry PY, Gauquelin G, Claustrat B, Sassolas G, Galliot J, Estanove S. Hemodynamic and hormonal responses to hypothermic and normothermic cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 132–139.
4. Greeley WJ, Bushman GA, Kong DL, Oldham HN, Peterson MB. Effects of cardiopulmonary bypass on eicosanoid metabolism during pediatric cardiovascular surgery. *Journal of Thoracic and Cardiovascular Surgery* 1988; **95**: 842–849.
5. Hashimoto K, Miyamoto H, Suzuki K, Horikoshi S, Matsui M, Arai T, Kurosawa H. Evidence of organ damage after cardiopulmonary bypass. The role of elastase and vasoactive mediators. *Journal of Thoracic and Cardiovascular Surgery* 1992; **104**: 666–673.
6. Reves JG, Karp RB, Buttner EE, Tosone S, Smith LR, Samuelson PN, Kreusch GR, Oparil S. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. *Circulation* 1986; **66**: 49–55.
7. Crystal GJ, Rooney MW, Salem MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. *Anesthesia and Analgesia* 1988; **67**: 211–218.
8. Lundgren O, Svanvik J. Mucosal haemodynamics in the small intestine of the cat during reduced perfusion pressure. *Acta Physiologica Scandinavica* 1973; **88**: 551–563.
9. Boros M, Takaichi S, Hatanaka K. Ischemic time-dependent microvascular changes and reperfusion injury in the rat small intestine. *Journal of Surgical Research* 1995; **59**: 311–320.
10. Ohri SK, Becket J, Brannan J, Keogh BE, Taylor KM. Effects of cardiopulmonary bypass on gut blood flow, oxygen utilization and intramucosal pH. *Annals of Thoracic Surgery* 1994; **57**: 1193–1199.
11. Cox CS, Zwischenberger JB, Fleming RYD, Alison WE, Myers T, Kurusz M, Herndon DN, Kramer GC. Ileal mucosal hypoperfusion during cardiopulmonary bypass. *Current Surgery* 1992; **49**: 507–510.
12. Ohri SK, Bowles CT, Siddiqui A, Khaghani A, Keogh BE, Wright G, Yacoub MH, Taylor KM. The effect of cardiopulmonary bypass on gastric and colonic mucosal perfusion: a tonometric assessment. *Perfusion* 1994; **9**: 101–108.
13. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Archives of Surgery* 1995; **130**: 423–429.
14. Gianotti L, Alexander JW, Fukushima R, Childress CP. Translocation of *Candida albicans* is related to the blood flow of individual intestinal villi. *Circulatory Shock* 1993; **40**: 250
15. Madara JL. Loosening tight junctions: lessons from the intestine. *Journal of Clinical Investigation* 1989; **83**: 1089–1094.
16. Baue AE. The role of the gut in the development of multiple organ dysfunction in cardiothoracic patients. *Annals of Thoracic Surgery* 1993; **55**: 822–829.
17. Koike K, Moore EE, Moore FA, Read RA, Carl VS, Banerjee A. Gut ischemia/reperfusion produces lung injury independent of endotoxin. *Critical Care Medicine* 1994; **22**: 1438–1444.
18. Biffl WL, Moore EE. Splanchnic ischaemia/reperfusion and multiple organ failure. *British Journal of Anaesthesia* 1996; **77**: 59–70.
19. Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *British Journal of Anaesthesia* 1995; **74**: 591–606.
20. Booker PD, Prosser DP, Franks R. Effect of hypothermia on rectal mucosal perfusion in infants undergoing cardiopulmonary bypass. *British Journal of Anaesthesia* 1996; **77**: 591–596.
21. Bove EL, West HL, Pashanik AM. Hypothermic cardiopulmonary bypass: a comparison between alpha and pH stat regulation in the dog. *Journal of Surgical Research* 1987; **42**: 66–73.
22. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; **19**: 1037–1040.
23. Miller TA. Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. *American Journal of Physiology* 1983; **245**: G601–G623.
24. Coombs RC, Morgan MEI, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. *Archives of Diseases in Childhood* 1990; **65**: 1067–1071.
25. Wong SN, Lo RN, Hui PW. Abnormal renal and splanchnic arterial Doppler pattern in premature babies with symptomatic patent ductus arteriosus. *Journal of Ultrasound Medicine* 1990; **9**: 125–130.
26. Tillous-Borde I, Mathe JC, Costil J, Fontaine JL. Une cause rare d'enterocolite ulcero–necrosante neo-natale: le syndrome de coarctation aortique. *Archives de Pediatrie* 1987; **44**: 377–378.
27. Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *British Journal of Anaesthesia* 1995; **74**: 149–154.
28. Rakugi H, Tabuchi Y, Nakamaru M, Nagano M, Higashimori K, Mikami H, Ogihara T, Suzuki N. Evidence for endothelin-1 release from resistance vessels of rats in response to hypoxia. *Biochemical and Biophysical Research Communications* 1990; **169**: 973–977.
29. Fukuda S, Taga K, Tanaka T, Sakuma K, Fujiwara N, Shimoji K, Fujihara H. Relationship between tissue ischemia and venous endothelin-1 during abdominal aortic aneurysm surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 1995; **9**: 510–514.
30. Bavaria JE, Furukawa S, Kreiner G, Ratcliffe MB, Streicher J, Bogen DK, Edmunds LHJ. Myocardial oxygen utilization after reversible global ischemia. *Journal of Thoracic and Cardiovascular Surgery* 1990; **100**: 210–220.
31. Bhatt SB, Hutchinson RC, Tomlinson B, Oh TE, Mak M. Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *British Journal of Anaesthesia* 1992; **69**: 298–303.
32. Yang Z, Richard V, von Segesser L, Bauer E, Stulz P, Turina M, Luscher TF. Threshold concentrations of endothelin-1 potentiate contractions to norepinephrine and serotonin in human arteries. *Circulation* 1990; **82**: 188–195.
33. Boyd O, MacKay CJ, Lamb G, Bland JM, Grounds RM, Bennett ED. Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. *Lancet* 1993; **341**: 142–146.
34. Landow L. Splanchnic lactate production in cardiac surgery patients. *Critical Care Medicine* 1993; **21**: S84–S91.
35. Hampton WW, Townsend MC, Schirmer WJ, Haybron DM, Fry DE. Effective hepatic blood flow during cardiopulmonary bypass. *Archives of Surgery* 1989; **124**: 458–459.

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Effects of dopamine on oxygen consumption and gastric mucosal blood flow during cardiopulmonary bypass in humans

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Summary

We investigated the effects of flow rate and dopamine on systemic oxygen delivery (DO_2), oxygen consumption ($\dot{V}O_2$) and gastric mucosal microcirculatory blood flow (gMCF), measured by laser Doppler flowmetry in 12 patients undergoing mild hypothermic (34 °C) cardiopulmonary bypass (CPB). The first intervention comprised increasing CPB flow rates from 2.4 to 3.0 litre min^{-1} m^{-2}, and the second intervention administering dopamine 6 μg kg^{-1} min^{-1}. Measurements were made before and 10 min after the start of one of the two interventions. The heart remained in cardioplegic arrest throughout the study. There were no significant differences in variables between the two baseline measurements preceding the interventions. The increase in CPB flow rate increased DO_2 and gMCF without affecting $\dot{V}O_2$. At constant flow rate, dopamine also increased gMCF with no change in $\dot{V}O_2$, DO_2 or mean arterial pressure. Our data suggested that dopamine had no flow-independent effect on $\dot{V}O_2$ and that it increased gMCF during constant flow hypothermic CPB. (*Br. J. Anaesth.* 1996; **77**: 603–606)

Keywords

Oxygen, consumption. Blood, flow. Gastrointestinal tract, mucosal perfusion. Heart, cardiopulmonary bypass. Surgery, cardiovascular. Pharmacology, dopamine.

We have shown previously that in patients undergoing cardiopulmonary bypass (CPB), dobutamine caused a flow-independent increase in oxygen consumption ($\dot{V}O_2$) without affecting gastric mucosal blood flow.[1] In common with dobutamine, dopamine increased $\dot{V}O_2$ in healthy volunteers with an intact circulation.[2] Unlike dobutamine, dopamine has been shown to increase splanchic[3] and gastric[3] mucosal blood flow in animals and humans. As gut mucosal ischaemia has been reported during cardiac surgery, and to correlate with postoperative morbidity,[5–7] administration of dopamine during cardiac surgery may be a means of ameliorating intraoperative splanchnic hypoperfusion in susceptible patients. However, the ability of dopamine to increase splanchnic blood flow has been challenged recently.[8,9] In pigs, dopamine did not increase total gastric blood flow during CPB.[8] However, dopamine may increase mucosal blood flow without affecting total gastric blood flow.

Therefore, the aims of this study were to investigate the effects of dopamine on $\dot{V}O_2$ and on gastric microcirculatory blood flow during constant flow CPB in patients undergoing cardiac surgery. We hypothesized that dopamine would be comparable with dobutamine in its flow-independent effects on $\dot{V}O_2$ but would differ in its effect on gastric microcirculatory blood flow. As we and others have shown, CPB provides a unique opportunity to study global and regional effects of drugs during constant flow.[1,10,11]

Patients and methods

After obtaining approval from the Ethics Committee of Essen University, and informed consent, we studied 12 patients requiring CPB for coronary artery bypass grafting. All patients received flunitrazepam 2 mg approximately 1 h before arriving in the operating room. Under local anaesthesia, a left radial arterial cannula and a flow-directed pulmonary artery catheter were inserted. Anaesthesia was induced with etomidate 0.15-0.30 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} and fentanyl 5–7 μg kg^{-1}, and maintained with 0.4–0.6 vol% isoflurance and 50% nitrous oxide in oxygen. Before CPB, additional fentanyl 0.25 mg, pancuronium 2 mg and flunitrazepam 0.2 mg were administered as needed. Fentanyl 0.25 mg and pancuronium 4 mg were added to the CPB prime, and 0.4 vol% isoflurane, added to the oxygenator air flow, was continued throughout the bypass period. Non-pulsatile pump flow (Stöckert, Munich, Germany) at a standard flow rate of 2.4 litre min^{-1} m^{-2} was maintained during extracorporeal circulation. Oxygenation was provided by a Cobe CML membrane oxygenator (Laboratories GmbH, Heimstetten, Germany). The asanguineous prime contained lactated Ringer's solution 100 ml, 10% hydroxyethylstarch 500 ml, 20% mannitol 100 ml and 8.4% sodium bicarbonate 100 ml. During CPB, blood temperature was maintained at 34 °C and packed cell volume was kept

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above 20% by transfusion of autologous packed red cells before bypass. Measurements were made after CPB had commenced, the aorta cross-clamped, the heart in cardioplegic arrest and after rectal and nasopharyngeal temperatures were within 0.8 °C of each other.

Gastric mucosal microcirculatory blood flow was studied using laser Doppler flowmetry (LDF) (MBF 3D, Moors Instruments Ltd, Devon, UK). The measurement probe, a fibreoptic wire, was inserted through the lumen of a nasogastric tube. The correct position of the nasogastric tube was confirmed by auscultation and aspiration of gastric contents. The correct position of the probe was verified by observing typical pulse synchronous oscillations. The frequency band used throughout the investigation was 14.9 kHz and the last 2 min of each period were averaged for the measurements. LDF uses the size and amount of the frequency shift caused by back-scattered laser beam to calculate microcirculatory flow.[12] LDF has been used experimentally to measure intestinal mucosal blood flow, and has been found to correlate with mucosal blood flow, as measured by standard techniques.[13] In addition to gastric microcirculatory blood flow, skin microcirculatory blood flow was studied by placing a second probe on the forehead of the patient.

Initial measurements were made at a flow rate of 2.4 litre min^{-1} m^{-2} (baseline 1). Flow was then increased to 3.0 litre min^{-1} m^{-2} (intervention 1), and repeat measurements were made 10 min later. Flow was then returned to and maintained at 2.4 litre min^{-1} m^{-2}, and measurements were repeated 5 min later (baseline 2). Subsequently, with no change in flow, dopamine was started at a rate of 6 μg kg^{-1} min^{-1} (intervention 2), and repeat measurements were made 10 min later. At each of these times, blood samples were obtained from sampling ports of the CPB cannulae for measurement of blood-gas tensions, and electrolyte and glucose concentrations, and haemodynamic variables were recorded. Blood-gas tensions were measured immediately at 37 °C. Total body oxygen delivery (DO_2) and $\dot{V}O_2$ were calculated according to standard formulae.

Non-parametric analysis of variance (Friedman) was used to test for differences between times. The Wilcoxon signed rank test, corrected for multiple comparisons (Bonferroni), was used to test for differences between each baseline and subsequent intervention, and between the two baseline values. Statistical significance was based on $P < 0.05$. Results are presented as mean (SD). The statistical program used was SPSS version 6.0 on an Accel (486DX33) Notebook computer (Accel Computers, Rockville, MD, USA).

Results

Patient data are summarized in table 1. The increase in flow rate from 2.4 to 3.0 litre min^{-1} m^{-2} increased DO_2 (approximately 20%) and gastric mucosal microcirculatory blood flow (gMCF) (table 2). Skin microcirculatory blood flow (sMCF), $\dot{V}O_2$ and mean arterial pressure (MAP) did not change significantly.

At unchanged flow rate, dopamine (table 2) increased gMCF ($P < 0.01$). There were no changes

Table 1 Patient characteristics (mean (range) or number). ACE=Angiotensin-converting enzyme

Age (yr)	63 (55–74)
Weight (kg)	76.5 (60–89)
Sex (M/F)	9/3
Preoperative medication (*n*):	
Beta blockers	–
Nitrates	7
ACE-inhibitors	1
Calcium antagonist	7
Digitalis glycosides	2

Table 2 Haemodynamic variables, gastric mucosal blood flow, oxygen delivery (DO_2) and oxygen consumption ($\dot{V}O_2$) during the two interventions (mean (SD). MAP=Mean arterial pressure; SVRI=systemic vascular resistance index; CVP=central venous pressure; sMCF=skin microcirculatory blood flow; gMCF=gastric mucosal microcirculatory blood flow. ***P<0.001 compared with preceding value

	Flow intervention		Dopamine (6 μg kg^{-1} min^{-1})	
	Before	After	Before	After
Flow rate (litre min^{-1} m^{-2})	2.4	3.0	2.4	2.4
$\dot{V}O_2$ (ml min^{-1} m^{-2})	82 (12)	87 (12)	80 (8)	79 (11)
DO_2 (ml min^{-1} m^{-2})	268 (23)	345 (28)***	275 (27)	284 (27)
MAP (kP)	9.1 (1.2)	10.1 (2.1)	10.1 (1.5)	9.6 (2.7)
SVRI (dyn cm^{-5} s m^{-2})	2127 (262)	2008 (419)	2414 (357)	2286 (745)
sMCF (units)	88 (51)	89 (45)	88 (34)	61 (22)
gMCF (units)	61 (33)	101 (40)***	62 (32)	115 (69)***

Table 3 Glucose and potassium concentrations, and rectal temperature during the two interventions (mean (SD))

	Flow intervention		Dopamine (6 μg kg^{-1} min^{-1})	
	Before	After	Before	After
Flow rate (litre min^{-1} m^{-2})	2.4	3.0	2.4	2.4
Glucose (mmol litre^{-1})	6.7 (1.2)	7.3 (71.2)	7.7 (1.6)	7.9 (1.5)
Potassium (mmol litre^{-1})	4.2 (0.4)	4.1 (0.3)	4.2 (0.2)	4.2 (0.2)
Hb (g litre^{-1})	78 (8)	80 (8)	80 (9)	83 (8)
Temperature (°C)	34.5 (0.5)	34.4 (0.4)	34.4 (0.3)	34.1 (0.4)

in DO_2, $\dot{V}O_2$, sMCF or MAP during this intervention.

Blood glucose concentrations increased throughout the study ($P < 0.05$) unrelated to the individual intervention. Potassium and haemoglobin concentrations, and body temperature did not change significantly (table 3).

Discussion

The principal findings of this study were: (1) at constant flow, dopamine did not increase $\dot{V}O_2$; (2) at constant flow, dopamine increased gastric mucosal blood flow; and (3) increasing flow rates increased gastric mucosal blood flow.

Our finding that dopamine increased mucosal blood flow is consistent with previous studies. Dopamine receptors have been identified in the human gastric mucosa.[14] When injected locally into the gastric submucosa, dopamine increased gastric mucosal blood flow, as assessed by laser Doppler flowmetry.[4] Furthermore, in the rat, dopamine exhibited a protective role in the stomach.[15] Our study demonstrated that dopamine, administered i.v. at clinically relevant doses, may increase gastric microcirculatory blood flow in humans during CPB, supporting the role of dopaminergic receptors in regulating gastric mucosal blood flow in humans.

In contrast with the increases in gastric microcirculatory blood flow during both increase in flow and dopamine infusion, skin microcirculatory blood flow did not increase during each intervention. Differences in baseline vasomotor tone or vascular reactivity between gastric mucosal and cutaneous vasculature, or both, may explain the different regional flow responses. To what extent differences in flow response are caused by redistribution of flow between regional circulations on the basis of a steal phenomenon cannot be determined by this investigation.

In two previus studies using a similar design, we found that during constant flow CPB, chronic pretreatment with beta adrenoceptor antagonists decreased $\dot{V}O_2$[10] and dobutamine increased $\dot{V}O_2$.[1] These findings suggest a flow-independent effect of catecholamines on $\dot{V}O_2$ during CPB. In contrast with our previous findings with dobutamine, dopamine did not increase $\dot{V}O_2$ during constant flow CPB. Whereas dobutamine 5–10 $\mu g\ kg^{-1}\ min^{-1}$ increased $\dot{V}O_2$ or energy expenditure in normal volunteers by 22–30%,[16 17] comparable doses of dopamine increased $\dot{V}O_2$ or energy expenditure by only 6–10%.[2 18 19] Thus dopamine appears to increase $\dot{V}O_2$ to a lesser extent than dobutamine. In these studies, both dopamine and dobutamine increased heart rate, stroke volume, cardiac output and, most likely, myocardial oxygen consumption. When the heart is in cardioplegic arrest and unable to respond mechanically to catecholamine stimulations (as in this study), catecholamines are likely to produce a smaller increase in $\dot{V}O_2$. In accordance with this hypothesis, dobutamine, administered in comparable doses, caused a 22–33% increase in $\dot{V}O_2$ in healthy volunteers[2 19] but only an 11% increase during CPB.[1] Conversely, the small 6–10% increase in $\dot{V}O_2$ during administration of dopamine in the presence of an intact circulation[2 19] would explain the lack of an increase in $\dot{V}O_2$ during constant flow CPB in this study.

However, our results may only apply to nonpulsatile flow conditions. In the presence of pulsatile flow the absolute and relative effects of dopamine on gastric and cutaneous microcirculations may differ.

Increasing flow rate increased gastric microcirculatory blood flow. As $\dot{V}O_2$ did not increase during this intervention, hypoperfusion is unlikely to have occurred at the lower flow rate. Although increasing flow rates may increase the likelihood of damage to blood components, our findings suggest that increasing flow rates may be a means of increasing gastric microcirculatory blood flow in patients at risk of splanchnic hypoperfusion.

Laser Doppler flowmetry has been used previously to measure mucosal microcirculatory blood flow in animals[20] and humans.[13] Whereas in the absence of CPB, mechanical heart activity and ventilatory excursions transmitted to the very sensitive measurement probe via the oesophagus do, at times, produce artefacts, with the heart in cardioplegic arrest during CPB such artefacts do not occur. Laser Doppler flowmetry may not be reliable when there are acute changes in haemoglobin concentration.[20] However, haemoglobin concentration did not change through our study.

Randomization of the sequence of interventions (i.e. flow variation and dopamine infusion) might have been preferable. However, as there are no data on the clearance of dopamine during hypothermia we chose not to randomize the sequence of interventions. The similar values before flow intervention and before dopamine infusion are evidence of stability, and of return to baseline conditions after flow intervention. In addition, in three patients in whom the duration of CPB allowed a repeat measurement 10 min after discontinuation of infusion of dopamine, the laser signal returned to near baseline values.

In conclusion, our data suggest that both increasing CPB flow rates and infusing dopamine during constant flow CPB did not affect $\dot{V}O_2$ but increased gastric microcirculatory blood flow. Patients at risk of gastric mucosal ischaemia may thus benefit from dopamine during CPB.

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References

1. Karzai W, Lötte A, Günicker M, Vorgrimler-Karzai U-M, Priebe H-J. Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass. *British Journal of Anaesthesia* 1996; 76: 5–8.
2. Ruttimann Y, Chioléro R, Jéquier E, Breitenstein E, Schutz Y. Effects of dopamine on total oxygen consumption and oxygen delivery in healthy men. *American Journal of Physiology* 1989; 259: E541–E546.

3. Robie NW, Goldberg LI. Comparative systemic and regional effects of dopamine and dobutamine. *American Heart Journal* 1975; **90**: 340–345.
4. Kaise M, Echizen H, Ishizaki T. Dopaminergic control of gastric mucosal blood flow in humans. *Digestive Diseases and Sciences* 1993; **38**: 1169–1174.
5. Fiddian-green RG. Gut mucosal ischemia during cardiac surgery. *Seminars in Thoracic and Cardiovascular Surgery* 1990; **2**: 389–399.
6. Niinikoski J, Kutilla K. Adequacy of tissue oxygenation in cardiac surgery: Regional measurements. *Critical Care Medicine* 1993; **21**: S77–S83.
7. Andersen LW, Landow L, Baek L, Jansen E, Baker S. Associatikon between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor-alpha concentrations in patients undergoing cardiopulmonary bypass. *Critical Care Medicine* 1993; **21**: 210–217.
8. Mackay JH, Feerick AE, Woodson LC, Lin C-Y, Deyo DJ, Uchida T, Johnston WE. Increasing organ blood flow during cardiopulmonary bypass in pigs: Comparison of dopamine and perfusion pressure. *Critical Care Medicine* 1995, **23**: 1090–1098.
9. Segal JM, Phang T, Walley KR. Low-dose dopamine hastens onset of gut ischemia in a porcine model of hemorrhagic shock. *Journal of Applied Physiology* 1992; **73**: 1159–1164.
10. Karzai W, Günnicker M, Vorgrimler-Karzai U-M, Freund U, Zerkowski H-R. The effects of beta-adrenoreceptor blockade on oxygen consumption during cardiopulmonary bypass. *Anesthesia and Analgesia* 1994; **79**: 19–22.
11. Videcoq M, Desmonts J-M, Marty J, Hazebroucq J, Langlois J. Effects of droperidol on peripheral vasculature: Use of cardiopulmonary bypass as a study model. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 370–374.
12. Stern MD. In vivo evaluation of microcirculation by coherent light scattering. *Nature (London)* 1975; **254**: 56–58.
13. Ahn H, Lindhagen J, Nilsson GE, Salerud EG, Jodal M, Lundgren O. Evaluation of laser flowmetry in the assessment of intestinal blood flow in cat. *Gastroenterology* 1985; **88**: 951–957.
14. Hernandez DE, Mason GA, Walker CH, Valenzuela JE. Dopamine receptors in human gastrointestinal mucosa. *Life Sciences* 1987; **41**: 2717–2723.
15. MacNaughton WK, Wallace JL. A role of dopamine as an endogenous protective factor in the rat stomach. *Gastroenterology* 1989; **96**: 972–980.
16. Green CJ, Frazer RS, Underhill S, Maycock P, Fairhurst JA, Campbell IT. Metabolic effects of dobutamine in normal man. *Clinical Science* 1992; **82**: 77–83.
17. Bhatt S, Hutchinson R, Tomlinson B, Oh T, Mak M. Effects of dobutamine on oxygen supply and uptake in healthy volunteers. *British Journal of Anaesthesia* 1992; **69**: 298–303.
18. Ruttimann Y, Schutz Y, Jequier E, Lemarchand T, Chioléro R. Thermogenic and metabolic effects of dopamine in healthy men. *Critical Care Medicine* 1991; **19**: 1030–1036.
19. Ensinger H, Weichel T, Lindner KH, Grünert A, Ahnefeld FW. Effects of norepinephrine, epinephrine, and dopamine infusions on oxygen consumption in volunteers. *Critical Care Medicine* 1993; **21**: 1502–1508.
20. Casadevall M, Panes J, Pique JM, Bosch J, Teres J, Rodes J. Limitations of laser-Doppler velocimetry and reflectance spectrophotometry in estimating gastric mucosal blood flow. *American Journal of Physiology* 1992; **263**: G810–815.

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Effects of rocuronium and vecuronium on intracranial pressure, mean arterial pressure and heart rate in neurosurgical patients

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Summary

We have evaluated the effects of a single bolus dose of rocuronium 0.6 mg kg^{-1} (group 1, $n = 10$) or vecuronium 0.1 mg kg^{-1} (group 2, $n = 10$) on intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP) and heart rate (HR) in 20 neurosurgical patients undergoing mechanical ventilation of the lungs during continuous sedation with sufentanil and midazolam. Before and after neuromuscular block using twice the ED_{90} of the blockers, ICP, MAP, CPP and HR were recorded continuously for 15 min. Treatment caused no significant changes in ICP, CPP or MAP and there was no evidence of histamine release. Mean maximum block in the rocuronium group was slightly less than that in the vecuronium group (95.9 (3.1) % *vs* 100%; ns) The difference between the two groups in onset time (rocuronium 142 (62) s, vecuronium 192 (64) s; $P = 0.04$) was significant. Patients in the rocuronium group showed a slight (7 (4) %) but significant ($P = 0.003$) increase in heart rate. (*Br. J. Anaesth.* 1996; **77**: 607–611)

Key words
Neuromuscular block, rocuronium. Neuromuscular block, vecuronium. Brain, intracranial pressure. Surgery, neurological. Cardiovascular system, effects. Heart, heart rate. Arterial pressure, drug effects.

For neurosurgery the use of drugs which do not increase or preferentially decrease intracranial pressure (ICP) is preferred. For emergency neurosurgery, rapid sequence intubation is often performed as fasting conditions in patients with subarachnoid haemorrhages, severe head injury or intracerebral bleeding are often unknown. Suxamethonium is often used to facilitate tracheal intubation because of its rapid onset, but it has the disadvantage of increasing intracranial pressure.[1] Other non-depolarizing agents such as vecuronium[1 2] and atracurium dibesylate[1 3–5] have no direct effect on ICP; however, their onset of action is considered too long for rapid sequence intubation. Rocuronium is a non-depolarizing neuromuscular blocking agent with a faster onset than all currently available non-depolarizing agents, approaching that of suxamethonium.[6 7]

There are no previous studies of the effects of rocuronium on cerebral dynamics. Because of the rapid onset of action of rocuronium,[8] we have compared the effects of rocuronium with those of vecuronium on ICP, mean arterial pressure (MAP), cerebral perfusion pressure (CPP) (= MAP − ICP) and heart rate (HR) in neurosurgical patients.

Patients and methods

After approval from the local Ethics Committee, we studied 20 ASA I–III patients, aged 18–65 yr. Patients known or suspected of having neuromuscular disorders, metabolic diseases, impaired renal function or impaired hepatic function were excluded. As osteoclastical trepanation interferes with the normal relationship between MAP and ICP, such patients were also excluded from this study. Five patients did not meet the inclusion criteria and these were replaced in order to have a total of 10 evaluable patients in each group. The investigation was performed in the neurosurgical intensive care unit, on postoperative or conservatively treated patients (table 1), after a stabilization period of at least 6 h without neuromuscular block. The lungs of all patients were ventilated in a volume-controlled mode with an air–oxygen mixture ($F_{I_{O_2}}$ = 0.3–0.4) and received, at least 6 h before the start of the study, continuous sedation with sufentanil 1–3 $\mu g\ kg^{-1}\ h^{-1}$ and midazolam 0.05–0.15 mg $kg^{-1}\ h^{-1}$ until at least the end of the study. An extradural probe (Gaeltec, Gaeltec Ltd, Scotland) or an intraventricular catheter (Cordis, Cordis Corporation, USA) was *in situ* for ICP measurements. Temperature (36–37 °C) and ventilation (end-tidal carbon dioxide concentration 4–4.5 kPa) were kept constant throughout the study.

In the intensive care unit, an arterial cannula, neuromuscular block monitoring equipment (Myotest MK II, Biometer Odense, Denmark) and an end-tidal carbon dioxide sensor were attached.

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Table 1 Patient data. Twenty neurosurgical patients received 2 × ED_{90} of either rocuronium or vecuronium. SAH=Subarachnoid haemorrhage

Patient No.	Diagnosis	Sex	ICP measurement	Age (yr)	Weight (kg)	Neuromuscular blocker
5	Intracerebral bleeding	M	Extradural	32	100	Vecuronium
6	Astrocytoma III	M	Intraventricular	42	100	Vecuronium
7	Comm. post. aneur., SAH	M	Intraventricular	32	95	Rocuronium
8	Comm. ant. aneur., SAH	M	Extradural	59	80	Vecuronium
9	Astrocytoma III	M	Extradural	42	79	Rocuronium
10	Aneur. middle cerebral art., SAH	F	Intraventricular	56	80	Rocuronium
12	Aneur. middle cerebral art., SAH	F	Intraventricular	27	55	Vecuronium
13	Meningioma temp. dext.	F	Extradural	34	75	Rocuronium
14	Aneur. middle cerebral art., SAH	F	Intraventricular	37	80	Vecuronium
15	Meningioma olfact.	M	Extradural	58	92	Vecuronium
16	Angioma parieto-occ. dext.	M	Extradural	43	85	Vecuronium
17	Aneur. comm. ant., SAH	M	Intraventricular	43	110	Rocuronium
18	Intracerebral haematoma	M	Extradural	25	65	Vecuronium
19	Intracerebral haematoma	F	Extradural	43	75	Vecuronium
20	Meningioma sphenoidale	F	Extradural	63	75	Rocuronium
21	Comm. ant. aneur., SAH	F	Extradural	51	75	Rocuronium
22	Comm. ant. aneur., SAH	M	Extradural	51	85	Rocuronium
23	Aneur. middle cerebral art., SAH	M	Intraventricular	51	85	Vecuronium
24	Comm. ant. aneur., SAH	M	Intraventricular	60	70	Rocuronium
25	Intracerebral haematoma	M	Extradural	41	75	Rocuronium

Neuromuscular block was monitored by supramaximal single twitch stimulation of the ulnar nerve at the wrist (single twitches of 0.2 ms duration at 0.1 Hz). Evoked responses were quantified mechanomyographically and recorded with a constant preload of 200–400 g on the adductor pollicis muscle to determine maximal neuromuscular response and onset time (time from administration of the neuromuscular blocking agent to 95% effect). HR, invasive MAP, end-tidal carbon dioxide, ICP and single twitch responses were allowed to stabilize for at least 10 min. Thereafter baseline variables (time T0: ICP_{T0}, MAP_{T0}, HR_{T0}, CPP_{T0}) and arterial blood samples were obtained for measurement of baseline Pa_{CO_2}. Patients in study group 1 received a single bolus dose of rocuronium 0.6 mg kg^{-1} and patients in study group 2 a single bolus dose of vecuronium 0.1 mg kg^{-1} i.v. As rocuronium is approximately six times less potent than vecuronium,[9–11] both doses represent twice the ED_{90}. HR, MAP, end-tidal carbon dioxide and ICP were recorded every minute for 15 min (time T1–T15) after administration of the neuromuscular blocking agent. Changes in ICP ($\Delta ICP_{Ti} = ICP_{Ti} - ICP_{T0}$), HR ($\Delta HR_{Ti} = HR_{Ti} - HR_{T0}$), MAP ($\Delta MAP_{Ti} = MAP_{Ti} - MAP_{T0}$) and CPP ($\Delta CPP_{Ti} = CPP_{TI} - CPP_{T0}$) were calculated for 15 min by subtracting the respective baseline values in both groups. Possible histamine-related reactions such as skin rashes, bronchospasms or severe (±20%) haemodynamic changes were recorded also.

Non-parametric analysis of variance (Friedman) was performed for HR, MAP, ICP and CPP in both the rocuronium and vecuronium groups followed by the multiple comparison Wilcoxon–Wilcox[12] if the Friedman test showed significance. Comparison of baseline variables (ICP_{T0}, MAP_{T0}, CPP_{T0}, HR_{T0}, Pa_{CO_2}) and neuromuscular variables in both groups was performed using the Mann–Whitney–Wilcoxon test. Results were considered statistically significant at $P < 0.05$.

Results

Characteristics of the 20 patients in the two groups are shown in table 2. Baseline variables did not differ significantly between the two groups. The time course of ΔICP, ΔCPP, ΔMAP and ΔHR during the 15-min study period is shown in figures 1 and 2. In the rocuronium group, the change in ICP from baseline varied from −3 to +4 mm Hg and in the vecuronium group from −4 to +2 mm Hg. There were no significant changes in ICP, MAP and CPP in each group even though MAP decreased slightly (4%) in the rocuronium group. Patients in the rocuronium group showed a slight (+7 (4) %) but significant ($P = 0.003$) increase in HR which peaked 5 min after drug administration and decreased thereafter to baseline values. HR did not change in patients in the vecuronium group. No patient had histamine-related symptoms or adverse clinical events. Mean maximum block in the rocuronium group was slightly lower than that in the vecuronium group (95.9 (3.1) % vs 100%; ns). The difference between the two groups in onset time (rocuronium 142 (62) s, vecuronium 192 (64) s; $P = 0.04$) was significant (table 2).

Table 2 Patient-related data and baseline variables (mean (SD or range) or number). n=10 for each group. ICP=Intracranial pressure, MAP=mean arterial pressure, HR=heart rate, CPP=cerebral perfusion pressure (CPP=MAP−ICP)

	Rocuronium	Vecuronium
Age (yr)	47.3 (32–63)	41.7 (25–59)
Height (cm)	173 (5.8)	168 (6.5)
Weight (kg)	81.9 (12.1)	81.7 (14.3)
Sex (M/F)	6/4	7/3
Baseline ICP (mm Hg)	14.2 (8.0)	15.9 (10.6)
Baseline MAP (mm Hg)	86.4 (9.9)	86.6 (11.0)
Baseline HR (beat min^{-1})	85.0 (12.0)	82.8 (17.6)
Baseline CPP (mm Hg)	72.2 (9.19)	70.7 (13.93)
Baseline Pa_{CO_2} (kPa)	4.4 (0.3)	4.4 (0.2)

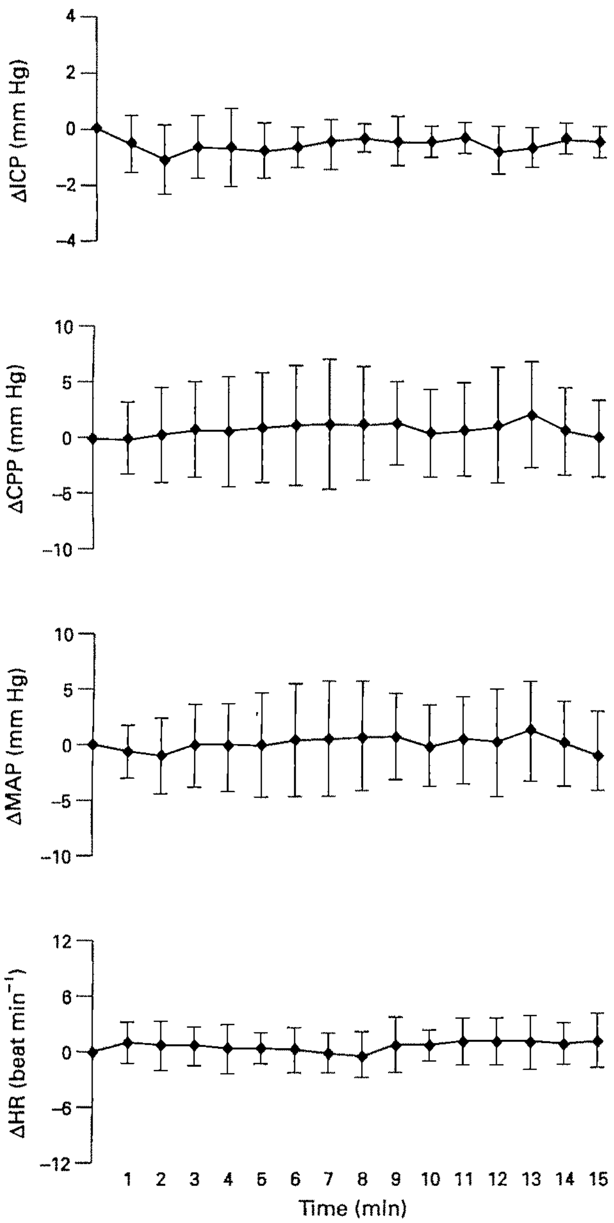

Figure 1 Changes from baseline of intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP) and heart rate (HR) after administration of vecuronium 0.1 mg kg^{-1} (mean, SD).

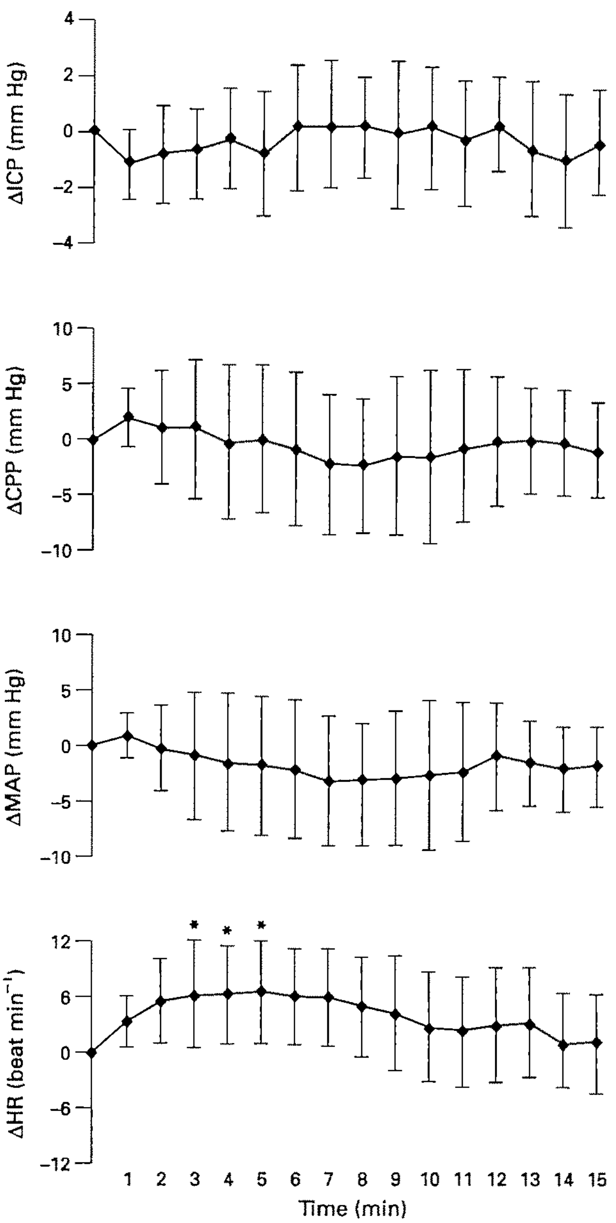

Figure 2 Changes from baseline of intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP) and heart rate (HR) after administration of rocuronium 0.6 mg kg^{-1} (mean, SD).*$P < 0.05$.

Discussion

In this study ICP was measured after administration of rocuronium 0.6 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} in adult neurosurgical patients undergoing mechanical ventilation and continuous sedation with sufentanil and midazolam. To avoid any impact of concomitant neuromuscular block during the study, only intermediate-acting neuromuscular blocking agents were used for tracheal intubation during the pre-study period. In this study we attempted to control and minimize confounding factors that could influence ICP. External stimuli such as noise, touch and tracheal suction which might alter ICP were either avoided or held constant during the study. Reliable monitoring of ICP with either an intraventricular or extradural probe was achieved as measurements were performed only after a stabilization interval of at least 6 h. Recording of ICP during surgery could have been confounded by surgical manipulation. ICP was measured extradurally in 12 and intraventricularly in eight patients. Although it has been shown that extradural pressure correlates closely with intraventricular pressure over a wide range in animals and in clinical practice,[13] we decided to include approximately the same number of patients with ICP measured extradurally and intraventricularly. As our study was undertaken in both six patients with extradural ICP measurement and four patients with intraventricular ICP measurement, a possible impact of measurement technique was excluded. However, both are accepted methods of ICP measurement and this study aimed to detect changes from baseline rather than absolute values. The non-parametric statistical analysis of choice to detect only changes in ICP from the baseline in a time span (figs 1, 2) was therefore the Friedman test.

We used sufentanil and midazolam for sedation.

There is controversy on the effects of sufentanil on ICP but recent studies have shown that sufentanil exerts minimal influence on ICP.[14] In patients sedated adequately with sufentanil, concomitant haemodynamic changes[15] are critical for adequate CPP, therefore, the infusion rate of sedating drugs remained unchanged before and during the study.

There was no significant change from baseline in MAP in the two groups during the 15-min study. The rocuronium group showed a transient increase in HR (fig. 1) which peaked 5 min after administration of the neuromuscular blocking agent. The fact that patients were stable before the beginning of the study might have contributed to the marked cardiovascular stability noted in this study. Increases in HR from baseline, probably because of a vagal blocking effect, did not exceed 7% and MAP did not decrease by more than 4% in the rocuronium group. These changes were not clinically important. Our results concur with a report on dose-related HR increases associated with rocuronium in humans.[16,17] As the drug possesses no ganglionic blocking effect or histamine-releasing properties,[18,19] a substantial decrease in MAP was unlikely. CPP is calculated from MAP and ICP, which were not influenced by either blocker and therefore CPP was not impaired.

A reduction in cerebral perfusion and venous blood return caused by coughing or poor synchronization with the ventilator results in increased cerebral oedema. In neurosurgical patients, neuromuscular block is important to avoid brisk bucking, straining and coughing during laryngoscopy and tracheal intubation. In neurological patients with severe head injuries or subarachnoid haemorrhages who are restless and demonstrate difficulty in artificial ventilation in spite of sedatives and analgesics, neuromuscular block may be the treatment of choice to prevent an increase in ICP.[20,21]

It is known that tubocurarine may increase ICP[22] by ganglionic block which may also produce arterial hypotension. If an increase in ICP occurs concomitantly with a decrease in MAP, a substantial decrease in CPP occurs. In patients with disturbed autoregulation, increased MAP after administration of pancuronium could be a disadvantage. Atracurium has the potential to release histamine, but in humans as in animals,[4,23] atracurium has been shown to have minimal effect on ICP. Vecuronium does not induce histamine release nor does it change MAP or HR. In patients with brain tumours, vecuronium had minimal effects on ICP,[2,24] which was consistent with our results. From the point of view of direct cerebral effects, non-depolarizing neuromuscular agents, such as pancuronium,[3,25] vecuronium[1,2,24] and atracurium, that do not increase ICP, are appropriate for use during neurosurgical procedures and for intubation. Good-to-excellent intubating conditions should exist to limit the increase in ICP which may be caused by intubation. The use of suxamethonium to facilitate tracheal intubation in neurosurgical patients has been associated with an increase in ICP for 4–6 min.[1,26] The mechanism of this effect has been ascribed to transient EEG desynchronization secondary to muscle fasciculation and concomitant increase in cerebral blood flow and cerebral blood volume[27–31] and to a transient increase in intra-abdominal pressure caused by muscle fasciculations leading to increased central venous pressure and intracerebral venous pressure.[32] Thus the increase in ICP is thought to be specific for depolarizing neuromuscular blocking agents. The use of suxamethonium therefore has been declining in clinical neuroanaesthetic practice, with the exception of emergency situations, such as the patient with a full stomach in whom rapid sequence induction is recommended.

Rocuronium is the first non-depolarizing neuromuscular blocking agent with a rapid onset (approaching that of suxamethonium) and good-to-excellent intubating conditions.[6,7] The results of our study suggest that rocuronium may be used for neurosurgical patients without the risks associated with suxamethonium.

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References

1. Ducey JP, Deppe SA, Foley KT. A comparison of the effects of suxamethonium, atracurium and vecuronium on intracranial haemodynamics in swine. *Anaesthesia and Intensive Care* 1989; 17: 448–455.
2. Rosa G, Sanfilippo M, Vilardi V, Orfei P, Gasparetto A. Effects of vecuronium bromide on intracranial pressure and cerebral perfusion pressure. A preliminary report. *British Journal of Anaesthesia* 1986; 58: 437–440.
3. Lanier WL, Milde JH, Michenfelder JD. The cerebral effects of pancuronium and atracurium in halothane-anesthetized dogs. *Anesthesiology* 1985; 63: 589–597.
4. Minton MD, Stirt JA, Bedford RF, Haworth C. Intracranial pressure after atracurium in neurosurgical patients. *Anesthesia and Analgesia* 1985; 64: 1113–1116.
5. Giffin JP, Litwak B, Cottrell JE, Hartung J, Capuano C. Intracranial pressure, mean arterial pressure and heart rate after rapid paralysis with atracurium in cats. *Canadian Anaesthetists Society Journal* 1985; 32: 618–621.
6. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology* 1993; 79: 913–918.
7. Huizinga AC, Vandenbrom RH, Wierda JM, Hommes FD, Hennis PJ. Intubating conditions and onset of neuromuscular block of rocuronium (Org 9426); a comparison with suxamethonium. *Acta Anaesthesiologica Scandinavica* 1992; 36: 463–468.
8. Puhringer FK, Khuenl Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1992; 75: 37–40.
9. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ohta Y. The neuromuscular effects of Org 9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; 75: 191–196.
10. Quill TJ, Begin M, Glass PS, Ginsberg B, Gorback MS. Clinical responses to Org 9426 during isoflurane anesthesia. *Anesthesia and Analgesia* 1991; 72: 203–206.
11. Wierda JM, De Wit AP, Kuizenga K, Agoston S. Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent. *British Journal of Anaesthesia* 1990; 64: 521–523.
12. Wilcoxon F, Wilcox RA. *Some Rapid Approximative Statistical Procedures*. In: New York: Amer Cyanamid Comp, 1964.
13. McDowall DG. Neurosurgical anesthesia and intensive care. *International Anesthesiology Clinics* 1978; 16: 16–43.

14. Weinstabl C, Mayer N, Richling B, Czech T, Spiss CK. Effect of sufentanil on intracranial pressure in neurosurgical patients. *Anaesthesia* 1991; **46**: 837–840.
15. Werner C, Kochs E, Bause H, Hoffman WE, Schulte am Esch J. Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. *Anesthesiology* 1995; **83**: 721–726.
16. Mellinghoff H, Lavaut E, Desmonts JM. Neuromuscular and cardiovascular properties of Org 9426. *Anesthesiology* 1991; **75**: 807.
17. Robertson EN, Hull JM, Verbeek AM, Booij LH. A comparison of rocuronium and vecuronium: the pharmacodynamic, cardiovascular and intra-ocular effects. *European Journal of Anaesthesiology* 1994; (Suppl. 9): 116–121.
18. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall IG. Effects of a new neuromuscular blocking agent (Org 9426) in anaesthetized cats and pigs and in isolated nerve–muscle preparations. *British Journal of Anaesthesia* 1989; **63**: 400–410.
19. Levy JH, Davis GK, Duggan J, Szlam F. Determination of the hemodynamics and histamine release of rocuronium (Org 9426) when administered in increased doses under N_2O/O_2-sufentanil anesthesia. *Anesthesia and Analgesia* 1994; **78**: 318–321.
20. McClelland M, Woster P, Sweasey T, Hoff JT. Continuous midazolam/atracurium infusions for the management of increased intracranial pressure. *Journal of Neuroscience Nursing* 1995; 27: 96–101.
21. Werba A, Weinstabl C, Petricek W, Plainer B, Spiss CK. Requisite muscle relaxation using vecuronium for tracheobronchial suction in neurosurgical intensive care patients. *Anaesthesist* 1991; **40**: 328–331.
22. Tarkkanen L, Laitinen L, Johanssohn G. Effects of d-tubocurarine on intracranial pressure and thalamic electrical impedance. *Anesthesiology* 1974; 40: 247.
23. Rosa G, Orfei P, Sanfilippo M, Vilardi V, Gasparetto A. The effects of atracurium besylate (Tracrium) on intracranial pressure and cerebral perfusion pressure. *Anesthesia and Analgesia* 1986; **65**: 381–384.
24. Stirt JA, Maggio W, Haworth C, Minton MD, Bedford RF. Vecuronium: effect on intracranial pressure and hemodynamics in neurosurgical patients. *Anesthesiology* 1987; **67**: 570–573.
25. McLeskey CH, Cullen BF, Kennedy RD, Galindo A. Control of cerebral perfusion pressure during induction of anesthesia in high-risk neurosurgical patients. *Anesthesia and Analgesia* 1974; **53**: 985–992.
26. Gabor AJ, Brooks AG, Scobey RP, Parsons GH. Intracranial pressure during epileptic seizures. *Electroencephalography and Clinical Neurophysiology* 1984; **57**: 497–506.
27. Lanier WL, Milde JH, Michenfelder JD. Cerebral stimulation following succinylcholine in dogs. *Anesthesiology* 1986; 64: 551–559.
28. Thiagarajah S, Sophie S, Lear E, Azar I, Frost EA. Effect of suxamethonium on the ICP of cats with and without thiopentone pretreatment. *British Journal of Anaesthesia* 1988; **60**: 157–160.
29. Cottrell JE, Hartung J, Giffin JP, Shwiny B. Intracranial and hemodynamic changes after succinylcholine administration in cats. *Anesthesia and Analgesia* 1983; **62**: 1006–1009.
30. Borman BE, Smith RB, Bunegin L, Albin MS. Does succinylcholine raise intracranial pressure? *Anesthesiology* 1980; 262
31. Minton MD, Grosslight K, Stirt JA, Bedford RF. Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockade. *Anesthesiology* 1986; **65**: 165–169.
32. Halldin M, Wahlin H. Effect of succinylcholine on intraspinal fluid pressure. *Acta Anaesthesiologica Scandinavica* 1959; **38**: 155–161.

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Interactions between suxamethonium and mivacurium or atracurium

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Summary

We have compared the dose–response relationships of suxamethonium, mivacurium and atracurium and examined the interactions of suxamethonium with mivacurium or atracurium in humans by isobolographic analysis. We studied 100 adult patients during fentanyl and thiopentone anaesthesia. Neuromuscular function was monitored using a Myograph 2000 (Biometer Co., Odense, Denmark). The dose–response curves were determined by probit analysis. Isobolographic and fractional analyses were used to assess quantitatively the combined effect of equipotent doses of suxamethonium, mivacurium and atracurium and to define the type of interaction between suxamethonium and mivacurium or atracurium. The ED_{50} values for suxamethonium, mivacurium and atracurium were 198.8 (95% confidence interval 190.7–206.9), 48.6 (45.4–51.8) and 202.1 (197.9–206.2) mg kg^{-1}, respectively. Isobolographic and fractional analyses of the suxamethonium–mivacurium and suxamethonium–atracurium combinations demonstrated antagonistic interactions. (*Br. J. Anaesth.* 1996; **77**: 612–616)

Key words

Interactions (drug). Neuromuscular block, suxamethonium. Neuromuscular block, mivacurium. Neuromuscular block, atracurium. Potency, anaesthetic, ED_{50}.

Mivacurium is a new, short-acting, non-depolarizing neuromuscular blocking agent of the benzylisoquinoline type.[1 2] It is hydrolysed by plasma cholinesterase *in vitro* at 70–88% the rate of suxamethonium.[3–5] Atracurium has an intermediate duration of action because of its chemical elimination by the Hofmann mechanism.[6] The effects of the interaction between suxamethonium and non-depolarizing neuromuscular blocking agents depend on the order of administration and doses used.[7–12] The interaction between non-depolarizing neuromuscular blocking agents by isobolographic analysis has been reported.[13–15] However, none of the data from these studies was subjected to interaction analysis.

In this study, we have compared the dose–response relationships for suxamethonium, mivacurium and atracurium and examined the interactions of suxamethonium with mivacurium or atracurium in humans by isobolographic analysis.

Patients and methods

After obtaining hospital Ethics Committee approval and informed consent, we studied 100 patients, ASA I or II, aged 17–59 yr, undergoing elective surgical procedures. No patient had any disease or metabolic abnormality known to alter neuromuscular transmission or was receiving any drug known or suspected of interfering with neuromuscular function.

Anaesthesia was induced with fentanyl 4–5 μg kg^{-1} and thiopentone 5 mg kg^{-1} i.v., without premedication, and maintained with a continuous infusion of thiopentone 10–15 mg kg^{-1} h^{-1} and intermittent boluses of fentanyl 1–2 μg kg^{-1}. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.8–5.3 kPa) via a face mask without tracheal intubation. Halogenated anaesthetics or nitrous oxide were not used.

The ulnar nerve was stimulated at the wrist with square-wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 10 s, using a Myotest DBS peripheral nerve stimulator (Biometer Co., Odense, Denmark). The resultant contraction of the adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Co., Odense, Denmark). Preload tension of the thumb was maintained at 300 g throughout the investigation. The first twitch (T1) of the TOF was considered the twitch height.

After stable recording of neuromuscular transmission had been established for a minimum of 30 min, patients were allocated randomly to receive suxamethonium, mivacurium, atracurium, suxamethonium and mivacurium or atracurium combination. The following predetermined doses of drugs were administered to subgroups of 20 patients: suxamethonium 150, 250 and 350 μg kg^{-1}; mivacurium 30, 50 and 70 μg kg^{-1}; atracurium 150, 200 and 250

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μg kg^{-1}; suxamethonium and mivacurium, respectively, 198 and 48.6 μg kg^{-1}, 247.5 and 60.8 μg kg^{-1}, 297 and 72.9 μg kg^{-1}; suxamethonium and atracurium, respectively, 198 and 202 μg kg^{-1}, 247.5 and 243.5 μg kg^{-1}, 297 and 285 μg kg^{-1}. Studies of the single-drug groups were concluded first, so that doses of the combination could be planned. From the dose–response curves of the neuromuscular agents administered alone, we determined the respective effective doses resulting in 50% reduction of twitch tension (ED$_{50}$). Subsequently, dose–response curves were obtained by administration of the following drug combinations in a constant dose ratio based on the ED$_{50}$ values of the single agent. For the suxamethonium–mivacurium combination, the following combinations were administered: 1 × ED$_{50}$ suxamethonium + 1 × ED$_{50}$ mivacurium; 1.25 × ED$_{50}$ suxamethonium + 1.25 × ED$_{50}$ mivacurium; and 1.5 × ED$_{50}$ suxamethonium + 1.5 × ED$_{50}$ mivacurium. Similar dose ratio combinations were used for the suxamethonium–atracurium combination.

All drugs were given over 5 s into a rapidly flowing i.v. infusion. In the combination group, drugs were injected simultaneously into two separate i.v. cannulae inserted in one arm. The neuromuscular response was recorded as maximum depression of T1, expressed as a percentage of the control value, in the arm opposite to that cannulated. When the maximum effect of the selected dose was reached (that is, when no further decrease in evoked response to three consecutive stimuli occurred), the study was terminated and anaesthesia continued as appropriate for surgery.

The percentage values for twitch depression in each group were transformed to probits and plotted against the logarithm of the dose.[16] Regression lines were compared using analysis of covariance. ED$_{50}$ values were calculated from the log–probit regression lines for each group. Using analysis of variance, we compared age, weight and height between the different groups. Unless otherwise specified, the results are expressed as mean (95% confidence intervals) and were considered significant when $P < 0.05$.

Isobolographic analysis[17 18] was used to define the type of interaction between suxamethonium and mivacurium or atracurium. This analysis has the advantage of being independent of the slopes of the dose–response curves, that is parallelism does not have to be established. It has been used to confirm the interactions between non-depolarizing neuromuscular blocking agents[14 15] and between other drugs.[19–21] If the ED$_{50}$ of a combination falls on the theoretical additive line, the effect of the drug mixture is additive. Points to the left of the theoretical additive line would be consistent with a synergistic interaction, whereas points to the right of the line would indicate an antagonistic interaction. Confidence intervals for each point were calculated from the variances of each component alone and were evaluated for statistical significance using the unpaired Student's *t* test.

Fractional analysis[22] was based on the expression of the component doses of the two agents of the combination as fractions of the doses that produce the same effect when given separately. Values near 1 indicate additive interaction, values greater than 1 imply antagonism and values less than 1 indicate synergism. This analysis was also used to confirm the interaction between non-depolarizing neuromuscular blocking agents.[14 15]

Results

Patient characteristics are shown in table 1; they did not differ between groups. The calculated ED$_{50}$ values for twitch depression were 198.8 (95% confidence interval 190.7–206.9), 48.6 (45.4–51.8) and 202.1 (197.9–206.2) μg kg^{-1} for suxamethonium, mivacurium and atracurium, respectively. The dose–response curves are shown in figures 1 and 2. The regression lines for suxamethonium, mivacurium, atracurium and the combinations did not deviate from parallelism. The slopes for suxamethonium alone, mivacurium alone, suxamethonium combined with mivacurium, and mivacurium combined with suxamethonium were, respectively, 5.4 (5.0–5.8), 3.2 (2.7–3.7), 7.2 (6.9–7.5) and 6.3 (5.8–6.8) (fig. 1). The slopes for suxamethonium alone, atracurium alone, suxamethonium combined with atracurium, and atracurium combined with suxamethonium

Table 1 Patient characteristics (mean (range or SD) or number). M–S=Combination of mivacurium and suxamethonium; A–S=combination of atracurium and suxamethonium. No significant differences between groups

	Mivacurium	Atracurium	Suxamethonium	M–S	A–S
Age (yr)	32.3 (20–53)	33.3 (17–55)	36.9 (19–61)	32.6 (19–55)	34.3 (19–59)
Weight (kg)	64.6 (11.5)	62.8 (9.8)	65.3 (7.2)	62.6 (11.7)	62.5 (9.6)
Height (cm)	168.4 (10.5)	165.8 (9.1)	166.8 (8.9)	168.1 (7.9)	165.6 (8.7)
Sex (M/F)	9/11	8/12	10/10	10/10	9/11

Table 2 Equipotent doses (ED$_{50}$) and 95% confidence intervals for mivacurium and suxamethonium administered alone and in combination in a fixed-dose ratio

	Mivacurium component		Suxamethonium component		
	Fraction of ED$_{50}$	Dose (μg kg^{-1})	Fraction of ED$_{50}$	Dose (μg kg^{-1})	Sum of fraction
Mivacurium	1	48.6 (45.4–51.8)	—	—	1
Suxamethonium	—	—	1	198.8 (190.7–206.9)	1
Combination	0.62	30.2 (28.6–31.8)	0.62	123.3 (119.2–127.4)	1.24

Table 3 Equipotent doses (ED_{50}) and 95% confidence intervals for atracurium and suxamethonium administered alone and in combination in a fixed-dose ratio

	Atracurium component		Suxamethonium component		
	Fraction of ED_{50}	Dose ($\mu g\ kg^{-1}$)	Fraction of ED_{50}	Dose ($\mu g\ kg^{-1}$)	Sum of fraction
Atracurium	1	202.1 (197.9–206.2)	—	—	1
Suxamethonium	—	—	1	198.8 (190.7–206.9)	1
Combination	0.59	119.2 (115.1–123.3)	0.59	117.3 (110.2–124.4)	1.18

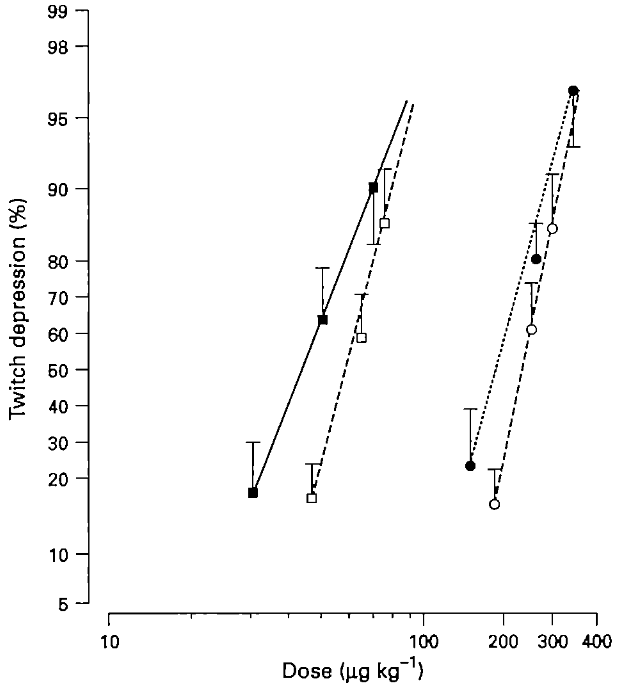

Figure 1 Log dose–probit plot for twitch depression for mivacurium with (□) or without (■) suxamethonium, and suxamethonium with (○) or without (●) mivacurium. Individual points represent mean (95% confidence intervals) twitch depression (% control) with each dose.

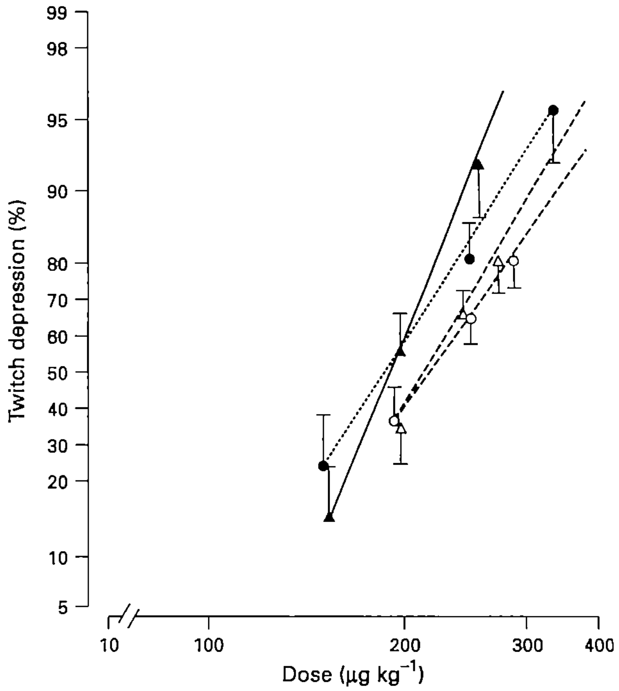

Figure 2 Log dose-probit plot for twitch depression for atracurium with (△) or without (▲) suxamethonium, and suxamethonium with (○) or without (●) atracurium. Individual points represent mean (95% confidence intervals) twitch depression (% control) with each dose.

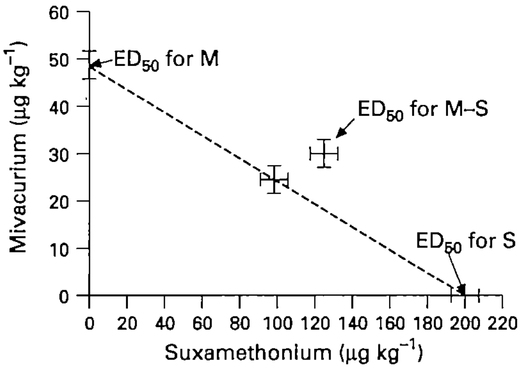

Figure 3 First-twitch ED_{50} isobologram for the interaction of mivacurium (M) and suxamethonium (S). The broken line connecting the single-drug ED_{50} points is the theoretical additive line; the point on this line is the theoretical additive point (95% confidence intervals). The experimentally determined ED_{50} dose (95% confidence intervals) of the mivacurium–suxamethonium (M–S) combination showed significant antagonistic effect ($P < 0.0005$).

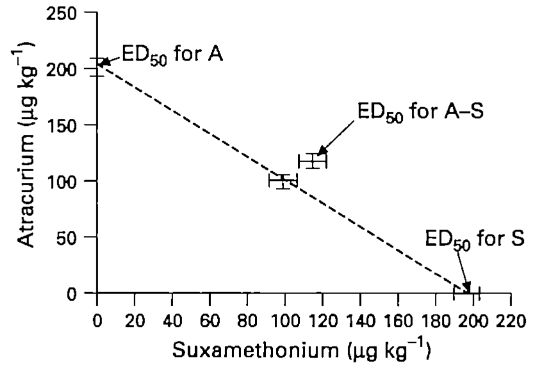

Figure 4 First-twitch ED_{50} isobologram for the interaction of atracurium (A) and suxamethonium (S). The broken line connecting the single-drug ED_{50} points is the theoretical additive line; the point on this line is the theoretical additive point (95% confidence intervals). The experimentally determined ED_{50} dose (95% confidence intervals) of the atracurium–suxamethonium (A–S) combination showed significant antagonistic effect ($P < 0.0005$).

were, respectively, 5.4 (5.0–5.8), 6.5 (6.2–6.8), 5.3 (5.1–5.5) and 5.7 (5.2–6.1) (fig. 2). The slopes and intercepts of the combined drugs were significantly different from those of the single drugs ($P < 0.05$).

Isobolographic analyses demonstrated antagonistic interactions with respect to the neuromuscular blocking activity of the suxamethonium and mivacurium or atracurium combinations (figs 3, 4). Fractional analyses of these interactions also demonstrated antagonism (tables 2, 3). The ED_{50} isobologram for the suxamethonium–mivacurium interaction is shown in figure 3. The experimentally determined ED_{50} value for the combination was 123.3 (119.2–127.4) $\mu g\ kg^{-1}$ for suxamethonium and 30.2 (28.6–31.8) $\mu g\ kg^{-1}$ for mivacurium. The theoretical additive ED_{50} value was calculated as 99.4 (91.3–107.5) $\mu g\ kg^{-1}$ for suxamethonium and 24.3 (21.2–27.4) $\mu g\ kg^{-1}$ for mivacurium. The confidence intervals of these points did not overlap and the result of Student's *t* test for potency ratio was significant ($P < 0.0005$).

The ED_{50} isobologram for the suxamethonium–atracurium interaction is presented in figure 4. The experimentally determined ED_{50} value for the combination was 117.3 (110.2–124.4) $\mu g\ kg^{-1}$ for suxamethonium and 119.2 (115.1–123.3) $\mu g\ kg^{-1}$ for atracurium. The theoretical additive ED_{50} value was calculated as 99.4 (91.3–107.5) $\mu g\ kg^{-1}$ for suxamethonium and 101 (96.8–105.2) $\mu g\ kg^{-1}$ for atracurium. The confidence intervals of these points did not overlap and the result of Student's *t* test for potency ratio was significant ($P < 0.0005$).

Discussion

We have found that isobolographic analyses demonstrated that the combination of suxamethonium and mivacurium or atracurium exerted greater antagonistic effects than those seen with either agent administered alone. Fractional analyses of these interactions also demonstrated antagonistic interactions, that is the effect of the combination was precisely that expected from the dose–response relations of the individual agents.

Suxamethonium was administered before or after non-depolarizing neuromuscular blocker in previous studies,[7–12] however, in this study suxamethonium and mivacurium or atracurium were administered simultaneously for isobolographic analysis. Potentiation of the effects of atracurium[8] and tubocurarine[10] was reported by prior administration of suxamethonium. In contrast, Walts and Dilien[7] noted the opposite for tubocurarine. Previous administration of suxamethonium had only minor effects on the following mivacurium block.[11 12] Pretreatment with mivacurium had a marked antagonistic effect on the development of subsequent depolarizing block produced by suxamethonium.[11] Small doses of suxamethonium might antagonize the partial block seen during recovery from atracurium, but larger doses usually enhanced the block.[9]

Szalados, Donati and Bevan[23] reported that small doses (0.15–0.25 mg kg^{-1}) of suxamethonium were associated with more twitch augmentation than higher doses. This was probably because twitch height was the algebraic sum of neuromuscular block and twitch augmentation. The large increases in twitch height observed with small doses suggested that twitch augmentation predominated with small doses, and block was more prominent if large doses were given. In this study the doses of suxamethonium (150, 250 and 350 $\mu g\ kg^{-1}$) were similarly small as those of twitch augmentation.

Traditionally, mivacurium or atracurium produce mainly competitive block of postsynaptic receptors. Such a block might be overcome by increasing the concentration of agonist usually, in clinical practice, by administration of neostigmine. However, suxamethonium also acted as an agonist and interacted with the same postsynaptic receptors, leading to the opening of ionic channels and depolarization of the membrane. In turn, this may initiate a muscle action potential and contraction. We interpreted our results collectively as the combination of suxamethonium and mivacurium or atracurium acted as the competitive antagonism at postsynaptic receptors.

Both mivacurium and suxamethonium are metabolized by plasma cholinesterase, suggesting that potentiation of block should occur in combination. However, recovery of twitch height during mivacurium block was even slightly shortened after suxamethonium in a patient with normal cholinesterase activity.[12] We also found that the antagonistic action of the combination of mivacurium and suxamethonium was similar to that of the combination of suxamethonium and atracurium which was not metabolized by plasma cholinesterase (figs 3, 4).

In this study, the ED_{50} value for suxamethonium (198.8 $\mu g\ kg^{-1}$) was similar to that reported by Smith, Donati and Bevan[24] (210 (190–230) $\mu g\ kg^{-1}$ during opioid–thiopentone–nitrous oxide anaesthesia). Naguib and colleagues[11] reported that the ED_{50} for suxamethonium was 86 $\mu g\ kg^{-1}$ by the single-dose technique during 1 MAC isoflurane anaesthesia, and Miller and colleagues[25] reported 88 $\mu g\ kg^{-1}$ by the cumulative dose technique during 1.25 MAC of isoflurane anaesthesia. Isoflurane may have potentiated neuromuscular block in these studies. We used the single-dose technique as the cumulative dose technique underestimated the potency of suxamethonium.[24]

The dose–response relationship of mivacurium and atracurium was estimated by means of the single-dose technique rather than by the cumulative method commonly used with neuromuscular blocking agents of long duration of action.[26] The possibility of higher ED_{50} and ED_{95} values of short-acting neuromuscular blocking agents generated by the cumulative method relative to the single-dose technique has been discussed by Gibson and colleagues.[27 28] We also used the single-dose technique for mivacurium and atracurium. Diefenbach and colleagues[29] reported that the ED_{50} of mivacurium was 48 $\mu g\ kg^{-1}$ during nitrous oxide and fentanyl anaesthesia, and this was similar to our result. Sokoll and colleagues[30] reported the ED_{50} of atracurium during nitrous oxide and fentanyl anaesthesia as 120 $\mu g\ kg^{-1}$. Naguib and colleagues[14] calculated an ED_{50} of 50.5 $\mu g\ kg^{-1}$ during isoflurane anaesthesia. Isoflurane potentiated neuromuscular block, but Sokoll and colleagues[30] used no inhalation agent. The only methodological difference between the study of Sokoll and colleagues and ours was the use of nitrous oxide for maintenance of anaesthesia. This raises the possibility of an interaction between nitrous oxide and atracurium.

We conclude that the interaction of suxamethonium and mivacurium or atracurium combination was the result of antagonistic action at the neuromuscular junction.

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References

1. Ali HH, Savarese JJ, Embree PB, Basta SJ, Stout RG, Bottros LH, Weakly JN. Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: comparison with vecuronium and atracurium. *British Journal of Anaesthesia* 1988; **61**: 541–546.
2. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology* 1988; **68**: 723–732.
3. Cook DR, Stiller RL, Weakly JN, Chakravorti S, Brandom BW, Welch RM. In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. *Anesthesia and Analgesia* 1989; **68**: 452–456.
4. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology* 1992; **77**: 785–805.
5. Brandom BW, Woelfel SK, Cook DR, Weber S, Powers DM, Weakly JN. Comparison of mivacurium and suxamethonium administered by bolus and infusion. *British Journal of Anaesthesia* 1989; **62**: 488–493.
6. Parker CJR, Jones JE, Hunter JM. Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. *British Journal of Anaesthesia* 1988; **61**: 531–540.
7. Walts LF, Dilien JB. Clinical studies of the interaction between d-tubocurarine and succinylcholine. *Anesthesiology* 1969; **31**: 39–44.
8. Stirt JA, Katz RL, Murray AL, Schehl DL, Lee C. Modification of atracurium blockade by halothane and by suxamethonium. A review of clinical experience. *British Journal of Anaesthesia* 1983; **55**: 71S–75S.
9. Scott RPF, Norman J. Effect of suxamethonium given during recovery from atracurium. *British Journal of Anaesthesia* 1988; **61**: 292–296.
10. Katz RL, Norman J, Seed RF, Contrad L. A comparison of the effects of suxamethonium and tubocurarine in patients in London and New York. *British Journal of Anaesthesia* 1989; **61**: 1041–1047.
11. Naguib M, Abdulatif M, Selim M, Al-Ghamdi A. Dose–response studies of the interaction between mivacurium and suxamethonium. *British Journal of Anaesthesia* 1995; **74**: 26–30.
12. Erkola O, Rautomn P, Meretoja OA. Interaction between mivacurium and succinylcholine. *Anesthesia and Analgesia* 1995; **80**: 534–537.
13. Naguib M, Abdulatif M. Isobolographic and dose–response analysis of the interaction between pipecuronium and vecuronium. *British Journal of Anaesthesia* 1993; **71**: 556–560.
14. Naguib M, Abdulatif M, Al-Ghamdi A, Selim M, Seraj M, El-Sanbary M, Magboul MA. Interactions between mivacurium and atracurium. *British Journal of Anaesthesia* 1994; **73**: 484–489.
15. Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, El-Bakry AK. Comparative potency of steroidal neuromuscular blocking drugs and isobolographic analysis of the interaction between rocuronium and other aminosteroids. *British Journal of Anaesthesia* 1995; **75**: 37–42.
16. Finney DJ. *Statistical Methods In Biological Assay*, 2nd Edn. London: Griffin, 1971; 21–57.
17. Tallarida RJ, Porreca F, Cowan A. Statistical analysis of drug–drug and site–site interactions with isobolograms. *Life Sciences* 1989; **45**: 947–961.
18. Berenbaum MC. What is synergy? *Pharmacological Reviews* 1989; **41**: 93–141.
19. Malmberg AB, Yaksh TL. Isobolographic and dose–response analyses of the interaction between intrathecal mu and delta agonists: Effects of naltrindole and its benzofuran analog (NTB). *Journal of Phamacology and Experimental Therapeutics* 1992; **263**: 264–275.
20. Malmberg AB, Yaksh TL. Pharamacology of the spinal action of ketorolac, morphine, ST-91, U50488H and L-PIA on the formalin test and an isobolographic analysis of the NSAID interaction. *Anesthesiology* 1993; **79**: 270–281.
21. Lee YW, Yaksh TL. Analysis of drug interaction between intrathecal clonidine and MK-801 in peripheral neuropathic pain rat model. *Anesthesiology* 1995; **82**: 741–748.
22. Bernbaum MC. Synergy, additivism and antagonism in immunosuppression. *Journal of Clinical and Experimental Immunology* 1977; **28**: 1–18.
23. Szalados JE, Donati F, Bevan DR. Effect of d-tubocurarine pretreatment on succinylcholine twitch augmentation and neuromuscular blockade. *Anesthesia and Analgesia* 1990; **71**: 55–59.
24. Smith CE, Donati F, Bevan DR. Dose–response curves for succinylcholine: single versus cumulative techniques. *Anesthesiology* 1988; **69**: 338–342.
25. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during forane and halothane anesthesia in human. *Anesthesiology* 1971; **35**: 509–514.
26. Donlon JV, Savarese JJ, Ali HH, Teplik RS. Human dose–response curves for neuromuscular blocking drugs: a comparison of two methods of construction and analysis. *Anesthesiology* 1980; **53**: 161–166.
27. Gibson FM, Mirakhur RK, Clarke RSJ, Lavery GG. Comparison of cumulative and single bolus dose techniques for determining the potency of vecuronium. *British Journal of Anaesthesia* 1985; **57**: 1060–1062.
28. Gibson FM, Mirakhur RK. Dose–response curves for pancuronium and tubocurarine. Comparison of single and cumulative dose techniques. *European Journal of Anaesthesia* 1987; **4**: 143–147.
29. Diefenbach C, Mellinghoff H, Lynch J, Buzello W. Mivacurium: dose–response relationship and administration by repeated injection or infusion. *Anesthesia and Analgesia* 1992; **74**: 420–423.
30. Sokoll MD, Gergis SD, Mehta M, Ali NM, Lineberry C. Safety and efficacy of atracurium (BW33A) in surgical patients receiving balanced or isoflurane anesthesia. 1983; **58**: 450–455.

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Midlatency auditory evoked potentials as indicators of perceptual processing during general anaesthesia

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Summary

We tested the hypothesis that midlatency auditory evoked potentials (MLAEP) can predict the occurrence of long latency AEP components (LLAEP), which are taken as evidence for perceptual processing. Forty-one patients undergoing cardiac surgery were anaesthetized with propofol and alfentanil. During several periods of surgery we recorded LLAEP. Peak-to-peak amplitude measures were used to determine if a particular LLAEP recording trace contained a recognizable waveform. Both before and after each LLAEP recording epoch, MLAEP and the spontaneous electroencephalogram (EEG) were recorded. Peak latencies and amplitudes of brainstem peak V and midlatency peaks Na, Pa, Nb, Pb and Nc, characteristic frequencies from the spontaneous EEG, mean arterial pressure (MAP) and nasopharyngeal temperature (*T*) were compared between recording epochs with and without clear LLAEP waveforms. These variables were also used in a discriminant analysis to predict the occurrence of an LLAEP waveform. Pa and Nb latencies were significantly shorter both before and after recording epochs in which an LLAEP waveform occurred, compared with epochs in which no LLAEP waveform occurred. Using a combination of up to six EEG, MLAEP, MAP and *T* measures, it was possible to predict the occurrence or absence of an LLAEP waveform with a sensitivity of 89% and specificity of 86%. We conclude that MLAEP components provide information on the possibility of perceptual processing during general anaesthesia, and thus may be relevant for monitoring depth of anaesthesia. (*Br. J. Anaesth.* 1996; **77**: 617–624)

Key words
Brain, evoked potentials. Monitoring, evoked potentials. Anaesthesia, depth.

Many studies on intraoperative memories suggest that auditory information processing may persist during general anaesthesia,[1] but there is still no standardized method for determining during operation whether or not an auditory stimulus is actually perceived. The availability of such a method is an essential prerequisite for monitoring anaesthetic depth. Auditory evoked potentials (AEP) provide a method for monitoring the transmission and processing of auditory stimuli from the cochlea to the cortex. The AEP consists of a series of waves that are characterized by their latency (the time of occurrence after sound onset) and amplitude. Brainstem auditory evoked potentials (BAEP), consisting of waves I–VII, occur within 10 ms after stimulus presentation, and reflect activation of the acoustic nerve and brainstem auditory structures. Midlatency AEP components (MLAEP) occur between 10 and 100 ms after sound onset. MLAEP components are termed N0, P0, Na, Pa, Nb, Pb and Nc, and are thought to be generated in thalamic and cortical auditory structures. MLAEP components are followed by long latency AEP components (LLAEP) which reflect activation of the association areas of the cerebral cortex. LLAEP components P1, N1 and P2 reflect the more cognitive aspects of information processing.[2] (No general agreement exists over the exact boundary to use between midlatency and long latency components. Theoretically, P1 and N1 are identical to Pb and Nc. In this article, labels P1 and N1 were used to indicate components elicited in an oddball paradigm, while labels Pb and Nc were used to indicate components elicited by clicks.)

Thornton has shown that BAEP components increase in latency with increased levels of volatile agents, whereas they remain unaffected by i.v. anaesthetics.[3] Latency and amplitude of MLAEP components have been found to show dose-related changes with general anaesthetics that were highly similar for inhalation and i.v. agents.[3 4] In addition, the decrease in Nb and Pb amplitude induced by anaesthesia was found to be reversed by surgical stimulation.[5] These results suggest that MLAEP components are related to responsiveness of the auditory pathways. However, their occurrence is

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insufficient evidence that the presented stimulus is actually perceived.[6] The purpose of this study was to investigate the relationship between MLAEP components and auditory perception. Evidence of such a relationship would provide further support for the usefulness of the MLAEP for routine monitoring of perceptual processing during anaesthesia.

Previous research on this relationship has focused on the isolated forearm technique (IFT) and implicit memory. In a study by Thornton and colleagues,[7] it was shown that responsiveness, as indicated by IFT, was associated with shorter latencies of MLAEP peak Nb. IFT measures the ability of a patient to respond to verbal commands during anaesthesia. Absence of a response may indicate unconsciousness, but it is also possible that the patient wanted to respond, but was unable. Furthermore, it may be difficult to distinguish general movements from a purposeful response to command. Another limitation is that this technique can only be used for a short period of time, to prevent ischaemia in the isolated arm. In a study by Schwender and co-workers,[8] Pa latency was 100% sensitive and 77% specific in predicting implicit memory for material presented during the intraoperative period. Although this supports the notion that MLAEP measures reflect some degree of perceptual processing, the results of implicit memory tests are not determined exclusively by the effects of anaesthesia on perceptual processing but also on memory processes. In addition, the results of implicit memory tests may also be affected by intermediate processes between the time of stimulus administration and the time of testing.

To circumvent these disadvantages of the IFT and implicit memory tests, we focused on LLAEP components as a possible way of obtaining evidence for perceptual processing. The N1 and P2 components, occurring approximately 100 to 200 ms after a stimulus, are associated with early discrimination processes. Their amplitudes are influenced not only by the physical features of the stimuli, but also by the subject's attention.[9] The P3 component is a task-related component, most typically elicited by an infrequent stimulus presented against a background of frequent, standard stimuli (the so-called oddball task). This component, which has a latency of 250–600 ms, reflects controlled stimulus processing and target detection, presumably associated with conscious awareness of the presented stimulus.[10] Evidently, recording of LLAEP components in addition to MLAEP components would create the possibility of relating early cortical MLAEP changes resulting from anaesthesia to variations in levels of perceptual and cognitive processing.

In this study, MLAEP and LLAEP were recorded during several periods of cardiac surgery with propofol–alfentanil anaesthesia. Our hypothesis was that MLAEP measures can predict the occurrence of LLAEP components (specifically the P1-N1-P2 complex), which is taken as the earliest evidence of perceptual processing. The predictive value of MLAEP measures was compared with that of mean arterial pressure, nasopharyngeal temperature and several spectral EEG measures.

Patients and methods

The study was performed at the Catharina Hospital, Eindhoven, and was approved by the local medical Ethics Committee. Informed consent was obtained from 41 patients (34 male) undergoing cardiac surgery. Mean age of the patients was 59 (range 38–74) yr. Two patients underwent aortic valve replacement and the others underwent coronary artery bypass grafting. Patients were premedicated approximately 2 h before surgery with morphine 10 mg s.c. Total i.v. anaesthesia was used with propofol and alfentanil. Anaesthesia was induced with a loading dose of propofol 2 mg kg^{-1} and alfentanil 100 $\mu g\ kg^{-1}$, given over 12 min; after this, anaesthesia was continued with infusion rates of propofol of 8 mg $kg^{-1}\ h^{-1}$ and alfentanil 4 $\mu g\ kg^{-1}\ min^{-1}$ for 10 min, then propofol 6 mg $kg^{-1}\ h^{-1}$ and alfentanil 3 $\mu g\ kg^{-1}\ min^{-1}$ for 10 min and finally propofol 4 mg $kg^{-1}\ h^{-1}$ and alfentanil 2 $\mu g\ kg^{-1}\ min^{-1}$ for maintenance. Pancuronium 8 mg was used to facilitate tracheal intubation. Additional pancuronium 8 mg was given at the start of cardiopulmonary bypass (CPB). The lungs were ventilated mechanically with air and oxygen to maintain end-tidal carbon dioxide pressure at 4 kPa. Oxygen saturation was monitored continuously. Increases in arterial pressure were counteracted with nitroglycerin or ketensine and decreases with administration of i.v. fluids, calcium or inotropic drugs, together with reduced doses of propofol and alfentanil. During CPB moderate hypothermia to 32 °C was used.

RECORDING PROCEDURE

Baseline recordings for both MLAEP and LLAEP were obtained on the morning of operation before patients were premedicated. During surgery MLAEP and LLAEP recordings were obtained during the following periods: before CPB (approximately 30 min after first incision); at the start of CPB; during CPB; at the end of CPB; and approximately 10 min after CPB.

In the event that surgery was too short to complete all recording series, period 3 was excluded. MLAEP and LLAEP were recorded successively during each of the above periods, as presented schematically in figure 1, because MLAEP components are typically evoked by presentation of auditory clicks, while LLAEP components are best elicited by tones with a much lower presentation rate. In addition, different filter settings are needed for these two types of AEP components, for which we used different EEG amplifiers. The total recording time in each recording period was limited to 22 min, as indicated in figure 1; typically it was about 15 min. The exact moment and duration of each recording epoch was dependent on the absence of disturbances caused by electrosurgery or the bypass pump.

An IBM-compatible 486 personal computer provided with a LabMaster analogue-to-digital (A/D) and digital-to-analogue (D/A) converter (Scientific Solutions, Solon OH) was used for presentation of MLAEP and LLAEP stimuli, control of the oddball task and acquisition of all neurophysiological signals, as described in the next sections.

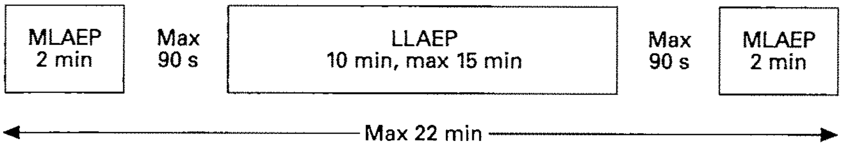

Figure 1 Schematic representation of MLAEP and LLAEP recording epochs.

LLAEP RECORDING AND PROCESSING

LLAEP were recorded during passive auditory oddball tasks. For baseline measurements, patients were instructed to ignore the stimuli. No specific instructions were given for the intraoperative recordings, because it was assumed that during anaesthesia patients would not be able to direct their attention towards any of the stimuli. Two tones of different pitch were presented binaurally through Nicolet Tip-10 insert earphones. The tones were 100-ms bursts of a digitally stored sine wave of 70 dB sound pressure level (SpL), with rise and fall times of 10 ms. Eighty percent of the stimuli were "standard" 1000-Hz tones, and 20% were "deviant" 2000-Hz tones. The inter-stimulus interval was 1044 ms. During two intraoperative oddball tasks (periods 1 and 4) five one-syllable words were presented repeatedly inter-mixed with the two types of tones. In these tasks the words had a probability of 0.15, compared with 0.70 for the standard tones and 0.15 for the deviant tones. After operation these words were tested for (covert) recognition, which will be reported in detail elsewhere (van Hooff and colleagues, in preparation). In the preoperative period, a total of 200 stimuli were presented. During surgery, 400–600 stimuli were presented because of a poorer signal-to-noise ratio.

For LLAEP processing, the raw electroencephalogram (EEG) was recorded from silver–silver chloride electrodes placed at Fz, Cz, Pz and two lateral positions C5 and C6, located midway between T3–C3 and T4–C4, respectively. Linked pre-auricular points served as reference. Recording and averaging were performed as described previously,[11] with the exception of filtering and artefact detection. In this study, the EEG signals were digitally filtered using a 33-point finite- impulse response bandpass filter with −3 dB cut-off frequencies of 2.7 and 8 Hz. The criteria for detecting an artefact were the occurrence of spikes greater than 110 μV, drift greater than 80 μV in a single trial or a difference in DC level in successive 250-ms epochs larger than 60 μV. The mean number of trials composing LLAEP in response to frequent tones, infrequent tones and words after artefact detection were 364 (SD 85), 87 (23) and 73 (14), respectively.

Peak amplitudes were determined for each individual waveform as being the most positive (for P1 and P2) and most negative (for N1) values in selected time windows based on the grand averages. P1 amplitudes were determined relative to the 200-ms pre-stimulus baseline, and N1 and P2 were determined with respect to their preceding peak (P1N1 and N1P2, respectively). P3 was not recognizable as a clear peak during anaesthesia and was therefore not quantified. Criteria for peak amplitudes were specified and used to judge whether or not a clear P1-N1-P2 complex could be distinguished in individual intraoperative recordings. Because LLAEP components were most clearly visible at Cz and because the recordings to frequent stimuli had the best signal-to-noise ratio, this was done for the Cz electrode position and the LLAEP to frequent tones only. When P1N1 and N1P2 amplitudes were larger than their median amplitudes (1.46 μV and 1.73 μV, respectively) and the correlation with an overall average waveform obtained by averaging all intraoperative LLAEP was larger than 0.55 (calculated over the first 800 ms of the response after tone-onset), then the recording was judged to be a clear LLAEP response, that is containing a recognizable P1-N1-P2 complex. The purpose of this assessment was to test if the presence of a clear LLAEP response could be predicted from the MLAEP.

MLAEP RECORDING AND PROCESSING

For MLAEP processing the raw EEG was recorded from Cz–A1 and Cz–A2, each referenced to Fpz. Recording and filtering of the EEG was performed as described previously.[12] Clicks were delivered with random inter-stimulus intervals, according to a Poisson distribution, with an average stimulation rate of 80 clicks s^{-1}. An important implication of using this distribution for random presentation of stimuli is that the effects of interfering stimuli are distributed equally over the entire sweep, independent of sweep length.[13 14] This results in a smoothing of the effect of interfering stimuli. We chose a sweep length of 270 ms for averaging of the MLAEP in this study to ensure that component Nc could be detected if present. Automatic detection of artefacts[12] was used to exclude sweeps containing artefacts from the averaging process. The MLAEP was not used in further processing if, because of the occurrence of artefacts, the total number of sweeps in the resulting average was lower than 3000 (corresponding to a net recording time of 38 s). From the resulting averages the latency and amplitude of brainstem peak V and of midlatency peaks Na, Pa, Nb, Pb and Nc were determined. Brainstem peak V was used to check if a response was actually present: if peak V could not be determined, the entire MLAEP waveform was not used in further processing.

PROCESSING OF THE SPONTANEOUS EEG

The raw EEG recorded for MLAEP averaging was also used for spectral analysis, using the CCSA software package developed in our group.[15] Before calculation of the spectra, the EEG was digitally low-pass filtered, using a 69-point moving average filter with a −3 dB cut-off frequency of 32 Hz. Spectra were calculated from 8-s epochs using 2-s overlapping of epochs, and applying a Blackman time window to prevent spectral leakage. Detection and rejection of epochs from the filtered EEG that contained artefacts was done with the same algorithm as was used for detecting artefacts in the MLAEP. If the occurrence of artefacts caused the total number of remaining epochs for a specific recording to be lower than six (corresponding to a net recording time of 38 s), that recording was not used in further processing. The features derived from the calculated spectra were median frequency, 95% spectral edge frequency and peak power frequency, and percentage delta (0–4 Hz), theta (4–8 Hz), alpha (8–14 Hz) and beta (>14 Hz) power. The resulting spectral features for each recording were averaged so that one set of EEG features remained for each set of MLAEP features.

Because the raw EEG was high-pass filtered at 5 Hz to enhance the quality of the MLAEP recordings, the calculated spectral features are higher than values reported in the literature as being necessary for surgical anaesthesia,[16 17] especially for median and peak power frequency. Percentage delta power is lower in our study.

RECORDING OF ARTERIAL PRESSURE AND TEMPERATURE

The values of mean arterial pressure (MAP) and nasopharyngeal temperature (*T*) were measured at the start and end of each MLAEP recording epoch. To avoid large physiological changes during the recordings, limits of acceptability were defined for the changes in MAP and *T*. When the difference in MAP and *T* values at the start and end of an MLAEP recording epoch exceeded the thresholds, as indicated in the first row of table 1, this MLAEP recording was excluded from further analysis. If neither MAP or *T* exceeded these thresholds, then for each MLAEP recording the average of MAP and *T* values obtained at the start and end of this recording epoch were calculated for inclusion in further analyses. When the differences in these average MAP and *T* values for the MLAEP recordings before and after each LLAEP recording epoch exceeded the thresholds, as indicated in the second row of table 1, then this set of MLAEP and LLAEP recordings was excluded from further analysis. This criterion implies that sets of MLAEP and LLAEP recordings for which there were no MAP or *T* values available, either before or after the LLAEP recording epoch, were also excluded from further analysis.

Table 1 Thresholds for mean arterial pressure (MAP) and nasopharyngeal temperature (*T*) for inclusion in the analysis. The threshold for changes in MAP was based on the maximally allowed range for MAP during CPB (40–70 mm Hg). The thresholds for changes in *T* were based on a maximally allowed cooling and rewarming rate of 0.5 °C min^{-1}

	MAP (mm Hg)	*T* (°C)
Maximally allowed difference between values obtained at start and end of MLAEP recording epoch	30	1
Maximally allowed difference between values obtained before and after LLAEP recording epoch	30	5

Systolic and diastolic arterial pressures were not included in the analysis, because during bypass no observations for these variables were available. Heart rate was also not included, partly because during CPB heart rate is zero, and partly because several patients were paced after CPB. This implies that heart rate contains no relevant information in these situations.

STATISTICAL ANALYSIS

MLAEP and EEG measures, MAP and *T* (all recorded both before and after each LLAEP recording epoch) were tested for differences between recording epochs in which an LLAEP occurred and epochs in which no LLAEP occurred. We used Wilcoxon's rank sum test for this comparison because of the low number of observations in the group consisting of recording epochs in which a reliable LLAEP occurred.

Predicting the occurrence of an LLAEP

Discriminant analysis was used to examine if it is possible to predict the occurrence of an LLAEP waveform in a specific recording epoch. Based on observations of MAP, *T* and MLAEP, and EEG features, a discriminant function was estimated that optimally separates the group of recording epochs in which an LLAEP occurred from the group of recording epochs in which no LLAEP occurred. Estimation of the optimal discriminant function was performed several times, using different sets of features, to compare the predictive power of the various available features. First, it attempted to predict the occurrence of an LLAEP using only the observations for MAP and *T* obtained at the start of each recording epoch. More variables were included for estimation of the discriminant function in subsequent analysis cycles. These added variables were the measures derived from the EEG (median, spectral edge and peak power frequency, and percentages of delta, theta, alpha and beta power) in the second cycle, the measures derived from the MLAEP (latencies and amplitudes of peaks V, Na, Pa, Nb, Pb and Nc) in the third cycle, and finally all MLAEP and EEG derived measures in the fourth cycle. These four cycles were repeated to include also the observations of the variables obtained at the end of each recording epoch.

In each cycle the discriminant analysis calculated the best linear combination of features from the total available data set by stepwise selection of variables. To prevent the resulting discriminant function from becoming difficult to interpret, we limited the number of variables to be included in the discriminant function to six in each cycle. The performance of the resulting discriminant function was tested after each cycle to see if its predictions agreed with the actual occurrence of an LLAEP waveform.

Table 2 Number of LLAEP recordings during the various periods of surgery. After selection=number of LLAEP recordings remaining after selecting those recordings for which both before and after the recording epoch, observations for MAP, *T*, MLAEP and EEG measures were present

	No. recordings		After selection	
	Total	Clear LLAEP	Total	Clear LLAEP
Total	176	44	52	9
Before CPB	35	19	8	3
At start of CPB	34	6	10	2
During CPB	33	—	11	—
At the end of CPB	34	11	4	1
After CPB	40	8	19	3

Because in this study we had only a limited amount of data available, we used the leave-one-out method for cross validation. This implies that when we have n data points, the discriminant function was calculated from $n-1$ data points and subsequently tested on the one remaining datum point. This was repeated n times so that each datum point was used once for testing. Performance was assessed in terms of sensitivity, specificity and accuracy. Sensitivity was defined as the fraction of epochs for which the occurrence of an LLAEP was predicted correctly by the discriminant function. Specificity was defined as the percentage of epochs for which the absence of an LLAEP was predicted correctly. Accuracy was defined as the percentage of epochs for which the occurrence or absence of an LLAEP was predicted correctly.

Results

In total, 176 LLAEP recordings were obtained during the 41 operations, of which 44 were judged as containing a clear LLAEP waveform (25%). Most of these clear LLAEP were recorded in the period before CPB, suggesting that perceptual processing occurred predominantly during this period. In table 2 the total number of LLAEP recordings obtained during the various periods of surgery are summarized. Table 2 also summarizes the number of recordings in each period of surgery for which both before and after the recording epoch complete observations for MLAEP, EEG, MAP and *T* were available. Of these remaining recordings, nine recording epochs obtained in nine different patients contained a clear LLAEP.

Examples of baseline and intraoperative LLAEP waveforms are presented in figure 2. Compared with preoperative LLAEP, intraoperative recordings were delayed and more positive going. N1, typical of preoperative recordings, decreased to or below prestimulus baseline levels during anaesthesia. A P3 response was generally absent in individual LLAEP traces. A more detailed description of the LLAEP results is presented elsewhere (van Hooff and colleagues, submitted). Examples of baseline and intraoperative MLAEP waveforms are presented in figure 3. Compared with baseline MLAEP waveforms, intraoperative MLAEP recordings showed longer latencies and smaller amplitudes. Compared with baseline EEG measures, intraoperative EEG

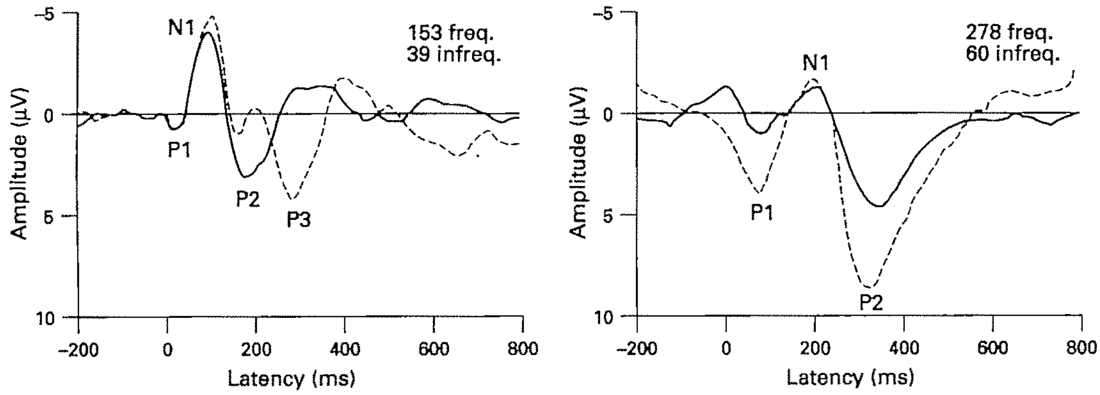

Figure 2 Examples of baseline (left) and intraoperative (right) LLAEP waveforms. Solid lines = responses to frequent stimuli, broken lines = responses to infrequent stimuli. Negativity is plotted upwards by convention.

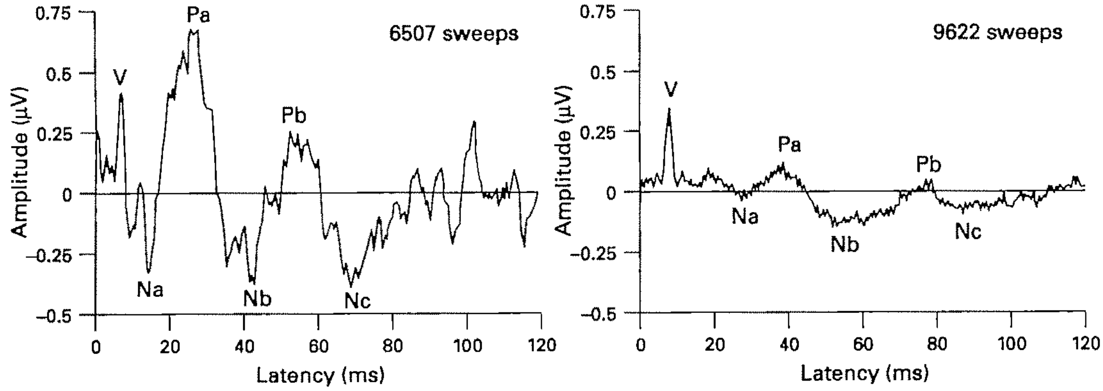

Figure 3 Examples of baseline (left) and intraoperative (right) MLAEP waveforms. Scaling of the axes is different from figure 2.

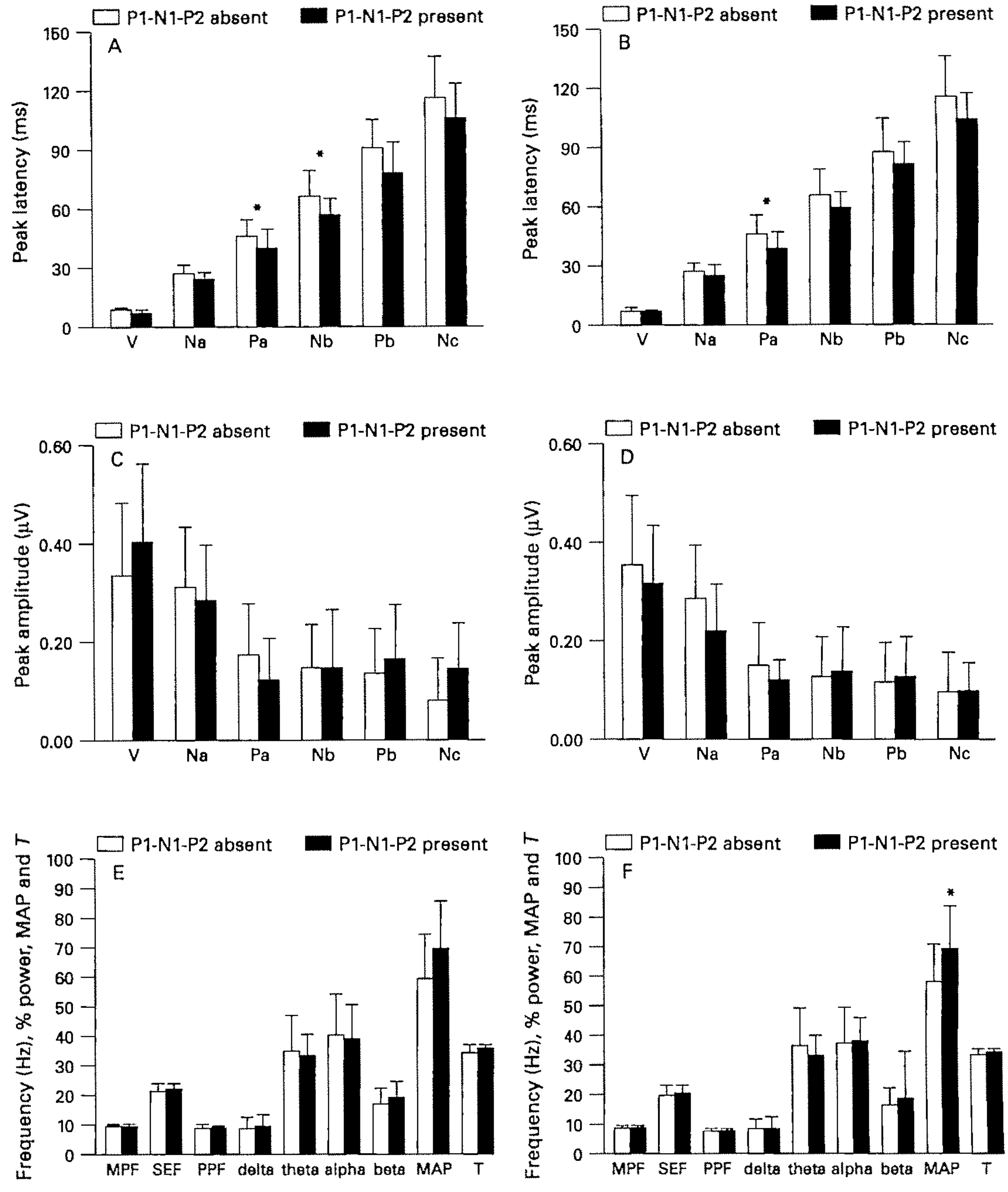

Figure 4 Mean (SD) values for MLAEP and EEG measures, mean arterial blood pressure (MAP) and nasopharyngeal temperature (T). Left column (A, C, E): MLAEP and EEG measures obtained before LLAEP recording epochs. Right column (B, D, F): MLAEP and EEG measures obtained after LLAEP recording epoch. First row (A, B): MLAEP peak latencies. Second row (C, D): MLAEP peak amplitudes. Third row (E, F): EEG spectral features, MAP and T.
$^*P < 0.05$ between recording periods (Wilcoxon rank sum tests).

measures showed a decrease in median, spectral edge and peak power frequencies, an increase in percentage delta and theta power, and a decrease in percentage beta power.

Mean (SD) values for MLAEP and EEG features, mean arterial pressure and nasopharyngeal temperature obtained before and after LLAEP recording epochs are presented in figure 4. Latencies of MLAEP peaks Pa and Nb were significantly shorter ($P = 0.050$ and $P = 0.045$, respectively) at the start of LLAEP recording epochs in which a clear LLAEP occurred, in comparison with recording epochs in which no clear LLAEP occurred. Latency of MLAEP peak Pa was significantly shorter ($P = 0.020$) at the end of LLAEP recording epochs in which a clear LLAEP occurred, compared with recording epochs in which no clear LLAEP occurred. Mean arterial pressure was significantly higher ($P = 0.042$) at the end of LLAEP recording epochs in which a clear LLAEP occurred, in comparison with recording epochs in which no clear LLAEP occurred.

The variables used in the discriminant function and its performance in predicting the occurrence of an LLAEP are summarized in Table 3. Adding only EEG features to the discriminant function did not improve the performance of the discriminant function beyond the performance of using only mean arterial pressure. Adding features from the MLAEP to the discriminant function improved specificity,

Table 3 Performance in terms of sensitivity, specificity and accuracy of different combinations of types of measured variables to predict the occurrence of an LLAEP. The first column indicates the group of variables available to the discriminant analysis, the second column indicates which of these variables were actually selected, in order of importance

Variable group	Variables used in discriminant function	Sens. (%)	Spec. (%)	Acc. (%)
Obtained before LLAEP recording epoch				
MAP + *T*	MAP	67	54	56
MAP + *T* + EEG	MAP	67	54	56
MAP + *T* + MLAEP	Lat Nb, MAP, amp V, amp Pb, amp Nc	67	74	73
MAP + *T* + MLAEP + EEG	Lat Nb, beta, amp Nc, amp V, MAP, sef	78	84	83
Obtained before (b) or after (a) LLAEP recording epoch				
MAP + *T*	MAP (a)	56	63	62
MAP + *T* + EEG	MAP (a)	56	63	62
MAP + *T* + MLAEP	Lat Pa (a), amp Nc (b), MAP (a), amp V (b), amp V (a), lat V (b)	78	81	81
MAP + *T* + MLAEP + EEG	lat Pa (a), beta (b), amp V (b) amp V (a), amp Nc (b), sef (b)	89	86	87

that is correct prediction of absence of an LLAEP waveform. Adding features from both the MLAEP and EEG improved sensitivity and specificity. Using MLAEP and EEG measures obtained both at the start and end of LLAEP recording epochs mainly improved sensitivity, that is correct prediction of the presence of an LLAEP waveform compared with using only variables obtained at the start of LLAEP recording periods.

Discussion

The hypothesis underlying this study was that MLAEP measures can predict the occurrence of LLAEP components during general anaesthesia. Our basic assumption was that the occurrence of LLAEP components can be taken as the earliest evidence for perceptual processing. It has been demonstrated that the N1 and P2 components reflect some level of perception[9 18] and that P3 reflects controlled stimulus processing and target detection.[10 19] These LLAEP components have in common that they are sensitive to the subject's psychological state, that is their amplitude and latency vary with attention, sleep or anaesthesia.[11 20–22] A study by Jessop and colleagues[23] showed a correlation between amnesia and presence or absence of P3.

When using an inter-stimulus interval of 1 s, and presenting a minimum of 200 stimuli (160 frequent and 40 infrequent stimuli), LLAEP recording during anaesthesia would require at least 3 min. Therefore, LLAEP themselves cannot be used for monitoring purposes, because rapid fluctuations in anaesthetic state cannot be detected. Instead, LLAEP can be used as a reference measure, providing information on whether or not auditory information processing actually occurs. If measures more suitable for monitoring, such as MLAEP components or spectral EEG measures, were to appear to be predictive with respect to the occurrence of LLAEP, this would be strong evidence for the use of these measures. It has been suggested that recording of MLAEP components also has the drawback that a relatively long acquisition time is needed.[24] A study by van de Velde, Cluitmans and Declerck[25] showed, however, that using random presentation of auditory stimuli, as was used in this study, may result in the acquisition of acceptable MLAEP waveforms within 40–60 s.

OCCURRENCE OF LLAEP WAVEFORMS

In agreement with our previous study,[11] P3 was not observed in individual intraoperative recordings, indicating that it is not likely that patients had awareness for the stimuli. Anaesthetic concentrations of fentanyl–isoflurane also suppressed the occurrence of a P3 response.[26] To date, only Plourde and colleagues[22] claimed to have observed a P3 subcomponent (P3a) during some periods of cardiac surgery during sufentanil anaesthesia. Although P3 is promoted frequently as being a promising measure to detect intraoperative awareness, it seems too easily abolished by surgical anaesthesia. Therefore, the presence of earlier LLAEP components, reflecting early perceptual processes (presumably automatically), was taken as a reference measure in this study. A clear P1-N1-P2 complex was present in 25% of intraoperative recordings. At first sight, this seems only a small proportion of all intraoperative recordings. However, these clear LLAEP were recorded in 28 of 41 patients, indicating that in 68% of all patients auditory processing persisted during some period of surgery.

Unfortunately, not all LLAEP obtained were preceded and followed by MLAEP and EEG recordings within the imposed time limit of 90 s. This was because of the restrictions imposed by external disturbances (e.g. electrosurgery), sudden changes during operation (e.g. onset of CPB) and anaesthetic or surgical intervention (e.g. defibrillation). Additionally, considerable effort was made to avoid large physiological changes during each series of recordings. After application of criteria to ensure the continuity of nasopharyngeal temperature and mean arterial pressure, 52 recording epochs, each comprising a series of MLAEP, LLAEP and MLAEP recordings as indicated in figure 1, remained for further analysis. From these 52 recordings, nine were judged as containing a clear LLAEP waveform (17%).

PREDICTIVE VALUE OF MLAEP AND EEG MEASURES

Pa and Nb latencies were shorter and MAP was higher when they were recorded close to LLAEP recording epochs comprising a clear LLAEP waveform than when they were recorded close to LLAEP recording epochs comprising no reliable LLAEP waveform (see fig. 4). This suggests a possible relationship between these measures and the presence of LLAEP components, that is the ability of higher level processing. This suggestion is supported by earlier observations of Thornton and colleagues[7] and Schwender and colleagues,[8] as described above. The predictive quality of Pa and Nb latencies in addition to MAP can further be derived from the fact that one or the other was always selected first in the discriminant functions. Because both variables are highly correlated they were not selected simultaneously by the discriminant analysis. MLAEP amplitudes, spectral EEG measures and nasopharyngeal temperature were not significantly different, whether or not the nearby LLAEP recording epochs comprised a clear LLAEP waveform. Nevertheless, discriminant analysis revealed that some of these variables in combination had predictive value with respect to the occurrence of clear LLAEP waveforms.

The results of our study indicate that both MLAEP and EEG measures may be used for predicting the occurrence of perceptual processing during anaesthesia. We found an accuracy of 87% in predicting the occurrence of an LLAEP waveform within a limited period of time, using MLAEP and EEG measures obtained at the start and end of that period of time. Accuracy was still 83% when only data obtained before the actual occurrence of an LLAEP waveform were used for this prediction.

In summary, we used LLAEP components for assessment of perceptual processing. The advantages of this technique are that it may also be used during longer periods of surgery, and that perceptual processing is assessed at the time it occurs. However, the long acquisition time needed for obtaining the LLAEP makes it unsuitable for routine monitoring. The results of our study provide additional support for the notion that the MLAEP and (to a lesser extent) the EEG may be used for routine monitoring of perceptual processing during anaesthesia. This may improve the conventional assessment of the risk of awareness based on clinical signs such as arterial pressure and heart rate.

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References

1. Ghoneim MM, Block RI. Learning and consciousness during general anesthesia. *Anesthesiology* 1992; **76**: 279–305.
2. Spehlmann R. *Evoked Potential Primer: Visual, Auditory, and Somatosensory Evoked Potentials in Clinical Diagnosis.* Stoneham, MA: Butterworths, 1985.
3. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; **8**: 89–107.
4. Thornton C, Newton DEF. The auditory evoked response: a measure of depth of anaesthesia. *Ballière's Clinical Anaesthesiology.* London: Ballière-Tindall 1989; **3**: 559–585.
5. Thornton C, Konieczko KM, Jones JG, Jordan C, Doré CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; **60**: 372–378.
6. Jessop J, Jones JG. Evaluation of the actions of general anaesthetics in the human brain. *General Pharmacology* 1992; **23**: 927–935.
7. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Doré CJ, Newton DEF, Jones JG. The auditory evoked response as an indicator of awareness. *British Journal of Anaesthesia* 1989; **63**: 113–115.
8. Schwender D, Kaiser A, Klasing S, Peter K, Pöppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 493–501.
9. Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology* 1987; **24**: 375–425.
10. Picton TW. The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology* 1992; **9**: 456–479.
11. Van Hooff JC, De Beer NAM, Brunia CHM, Cluitmans PJM, Korsten HHM, Tavilla G, Grouls R. Information processing during cardiac surgery: an event related potential study. *Electroencephalography and Clinical Neurophysiology* 1995; **96**: 433–452.
12. De Beer NAM, van de Velde M, Cluitmans PJM. Clinical evaluation of a method for automatic detection and removal of artifacts in auditory evoked potential monitoring. *Journal of Clinical Monitoring* 1995; **11**: 381–391.
13. Krausz HI. Identification of nonlinear systems using random impulse train imputs. *Biological Cybernetics* 1975; **19**: 217–230.
14. Cluitmans PJM, Beneken JEW. Non-linear analysis of sensory evoked potentials. *Proceedings of the 13th Annual International Conference of the IEEE Engineering in Medicine and Biology Society* 1991; 13: 419–420.
15. Van de Velde M, Cluitmans PJM. *EEG Analysis for Monitoring of Anesthetic Depth.* EUT-report 91–E–254, ISBN 90–6144–254–0. Eindhoven: Eindhoven University of Technology, 1991.
16. Schwilden H, Stoeckel H, Schüttler J. Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. *British Journal of Anaesthesia* 1989; **62**: 290–296.
17. Vernon J, Bowles S, Sebel PS, Chamoun N. EEG bispectrum predicts movement at incision during isoflurane or propofol anesthesia. *Anesthesiology* 1992; 77: A502.
18. Picton TW, Hillyard SA, Krausz HI, Galambos R. Human auditory evoked potentials. I: Evaluation of components. *Electroencephalography and Clinical Neurophysiology* 1974; **36**: 179–190.
19. Pritchard WS. Psychophysiology of P300. *Psychological Bulletin* 1981; **89**: 506–540.
20. Näätänen R, Mitchie PT. Early selective attention effects on the evoked potential. A critical review and reinterpretation. *Biological Psychology* 1979; **8**: 81–136.
21. Campbell K, Bell I, Bastien C. Evoked potential measures of information processing during natural sleep. In: Broughton R, Ogilvie R, eds. *Sleep, Arousal and Performance.* Cambridge: Birkhauser Boston, 1992; 88–116.
22. Plourde G, Joffe D, Villemure C, Trahan M. The P3a wave of the auditory event-related potential reveals registration of pitch change during sufentanil anesthesia for cardiac surgery. *Anesthesiology* 1993; **78**: 498–509.
23. Jessop J, Griffiths DE, Furness P, Jones JG, Sapsford DJ, Breckon DA. Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide. *British Journal of Anaesthesia* 1991; **67**: 524–531.
24. Munglani R, Andrade J, Sapsford DJ, Baddeley A, Jones JG. A measure of consciousness and memory during isoflurane administration: the coherent frequency. *British Journal of Anaesthesia* 1993; **71**: 633–641.
25. Van de Velde M, Cluitmans PJM, Declerck AC. Optimization of stimulation frequency in middle latency auditory evoked potentials in humans. *Technology and Healthcare* 1993; **1**: 340–341.
26. Plourde G, Picton TW. Long-latency auditory evoked potentials during general anesthesia: N1 and P3 components. *Anesthesia and Analgesia* 1991; **72**: 342–350.

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Effect of racemic mixture and the (S+)-isomer of ketamine on temporal and spatial summation of pain

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Summary

We have compared the analgesic efficacy of the racemic mixture and the stereoisomer (S+) of the NMDA antagonist ketamine. In a double-blind, three-way crossover, placebo-controlled study, we assessed the following: pain evoked by small/large area pressure stimuli, pain detection threshold and pain ratings to small/large area of heat stimuli, pain detection threshold and pain rating to heat stimuli of brief/long duration, summation pain threshold and pain ratings to repeated heat/electrical stimuli, side effects and reaction time. Plasma concentrations of 350 ng ml^{-1} for ketamine (racemic) and 180 ng ml^{-1} for ketamine (S+) were tried. We found that ketamine (racemic) prolonged the reaction time more than ketamine (S+). Both drugs affected pain caused by repeated stimuli or stimuli of long duration equally or more than a single stimulus of short duration. They also affected pain evoked from large areas equally or more than pain evoked from small areas. The (S+)-isomer was approximately twice as potent as the racemic mixture of ketamine in inhibiting central summation. (*Br. J. Anaesth.* 1996; **77**: 625–631)

Key words
Anaesthetics i.v., ketamine. Pain, mechanism. Pain, experimental. Pharmacokinetics, stereoisomers. Pharmacokinetics, ketamine.

Several studies have indicated that anaesthetic agents are less effective in blocking pain caused by repeated/prolonged stimuli than pain caused by a single stimulus, and less effective in blocking stimuli covering large areas than stimuli covering small areas.[1–5] Increased pain caused by repetition is termed temporal summation and increased pain as a result of activation of a large area is termed spatial summation.

Wind-up (increased and prolonged firing after repeated stimulation) in animal dorsal horn neurones[6–8] is probably the mechanism underlying temporal summation in humans. The mechanism behind spatial summation is less clear but is presumably a result of convergence on central neurones. Techniques to investigate wind-up are needed to assess the effect of different anaesthetic drugs on this mechanism in humans. Psychophysical and electrophysiological techniques have been established to assess temporal[9–11] and spatial[12] summation in humans.

Animal experiments have shown that NMDA antagonists inhibit wind-up.[12 13] In human studies, NMDA antagonists (ketamine, dextromethorphan) were found to attenuate temporal summation.[10 14] Unfortunately, few NMDA antagonists are available for human use and the existing drugs have severe psychomimetic side effects. Commercially available ketamine is a racemic mixture. In animal experiments the stereoisomer, ketamine (S+), has proved to be 2–3 times more potent but less psychoactive than the (R−)-isomer.[15] In a human study the (S+)-isomer was four times more potent than the (R−)-isomer for management of postoperative pain.[16] Therefore, the (S+)-isomer offers clinically useful advantages if an equipotential dose causes less side effects than the racemic mixture.

The aim of this double-blind, placebo-controlled human study was to use psychophysical techniques to determine the analgesic potency of ketamine (racemic) and ketamine (S+) on temporal and spatial summation and to compare potency and side effects.

Subjects and methods

We studied 12 paid, healthy students (mean age 27.1 (range 23–41) yr). Mean weight was 69.8 kg (range 58–86 kg). Informed consent according to the Helsinki Declaration was obtained and the study was approved by the Regional Scientific Ethics Committee, Bern.

I.v. infusion of NaCl–glucose was started before testing. Pulse oximetry (Sp_{O_2}), ECG and non-invasive arterial pressure were monitored during the study. Skin temperature at the lateral aspect of the

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forearm was measured by a medical precision thermometer (Therm 3480-6, Holzkirchen, Deutschland). Mean reaction time to five 1000-Hz tone stimuli was determined.

STIMULATION AND THRESHOLDS

Heat stimulation

The heat stimulator had a circular contact surface with a diameter of 20 mm (314 mm^2). This surface consisted of a thin copper foil placed on top of a thermofoil (Minco Products, Inc.), being a resistive heating element in principle (fig. 1). As the mass of the heating element was low, rapid increases in temperature were obtained (30 °C s^{-1}). The thermofoil was maintained at a constant baseline temperature (35 °C) by adjusting the current passing through the element. Temperature was calibrated by the medical precision thermometer. To obtain active cooling of the skin after each stimulation, a relatively large aluminium block was placed behind the thermofoil. This block was maintained at a constant temperature of 10 °C by a Peltier device and cooling water. This resulted in a skin cooling rate of up to 15 °C s^{-1}. Five identical heat stimulators were controlled individually and the areas activated by one, two, three, four and five thermodes were 314 mm^2, 628 mm^2, 942 mm^2, 1256 mm^2 and 1570 mm^2, respectively. The circular thermodes were placed on a line with a centre-to-centre distance of 50 mm. Heat pulses were delivered to the lateral aspect of the forearm without preparing the skin in any way. The inter-stimulus time was distributed randomly between 15 and 20 s.

Spatial summation

This stimulation procedure investigated if the drugs affected small and large areas in a similar way. Spatial summation was investigated by detection of the thermal pain threshold to one and five thermodes (314 and 1570 mm^2, respectively). The heat pain detection threshold was determined as the point where thermal sensation became painful. Peak temperature was increased automatically in steps of 0.5 °C until the threshold was reached. The stimulus was increased by 8 °C s^{-1} and maintained at the peak temperature for 2 s.

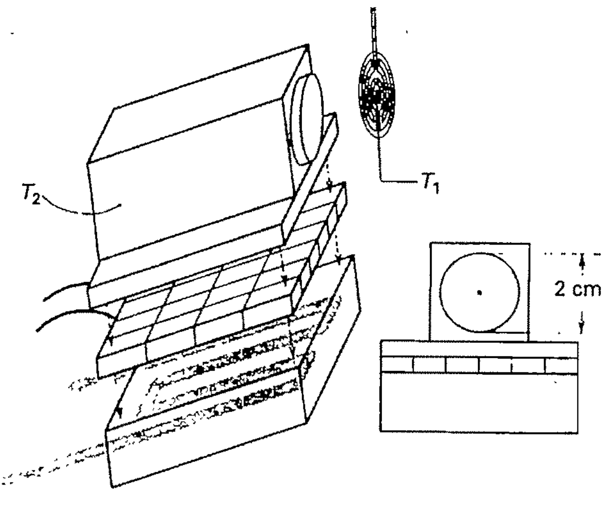

Figure 1 Schematic drawing of the thermal stimulator used in this study. The heat foil is maintained at a baseline temperature of, for example 35 °C (*T1*). The heat foil is glued (by thermal conductive glue) to an aluminium block maintained at a temperature of 10 °C (*T2*). This controlled cooling temperature is obtained by a Peltier device which is again cooled by water.

Temporal summation

This stimulation procedure determined if the drugs affected single and repeated stimuli in the same way, and short and long duration stimuli in a similar way. Temporal summation was investigated using a single thermode (314 mm^2) and five pulses delivered at 0.66 Hz (rise time 30 °C s^{-1}). The heat summation pain threshold was determined as the temperature at which the subject reported the pain to increase during the course of five stimuli.[11] Temperature was increased automatically in steps of 0.5 °C until the summation threshold was reached.

Another method of investigating temporal summation was to change the duration of the heat pulse. Volunteers were stimulated with one and five thermodes at a supra-threshold temperature of 50 °C in two ways: (1) 50 °C of one thermode was reached at 8 °C s^{-1} and then immediately returned to baseline. Pain intensity was rated on a VAS scale; (2) 50 °C of one and five thermodes was reached at 8 °C s^{-1} and maintained for 2 s and then returned to baseline. Pain intensity was rated on a VAS scale.

Electrical stimulation

This stimulation procedure examined if the drugs affected single and repeated stimuli in a similar manner. A constant current, computer-controlled stimulator (Aalborg University, Denmark) was used for percutaneous electrical stimulation of the sural nerve using a electrode with two silver–silver chloride electrodes separated by 20 mm (13L20, Dantec, Denmark). Five constant current 1-ms pulses supplied rectangularly at 200 Hz were defined as a "single stimulus". When this single stimulus was repeated five times at 2 Hz, it was defined as "repeated stimuli". The electrical summation pain threshold to repeated stimuli was determined as the point at which the subject felt an increasing sensation during the five stimuli[11] eventually resulting in pain. The intensity was increased in steps of 1 mA until the summation threshold was reached. At least 10 s elapsed between individual stimuli. The VAS rating to 1.2 times the baseline summation pain threshold was determined.

Pressure stimulation

This stimulation procedure investigated if the drugs affected small and large areas in a similar way. Pressure was applied using an electronic pressure algometer (Somedic AB, Stockholm, Sweden). Pressure pain detection and tolerance thresholds were determined using two different probe areas

(6.0 mm and 10.8 mm diameter, 28 mm^2 and 92 mm^2, respectively) applied at the second and third finger pulps of the left and right hand. Pressure was increased with a fixed rate of 50 kPa s^{-1} corresponding to 1.4 N s^{-1} and 4.6 N s^{-1} for the small and large areas, respectively. Ten to 15 s elapsed between stimuli.

MEDICATION

Volunteers received ketamine (racemic), ketamine (S+) or placebo (saline) in a randomized, double-blind, crossover design. Ketamine (racemic and S+) was administered by a target-controlled infusion system. This consisted of a computer connected to a Harvard 22 (Harvard Apparatus, South Natick, MA, USA) infusion pump with a serial interface. The pharmacokinetic variables for ketamine reported by Domino and co-workers[17] were programmed into the software Stanpump (Stanpump is available at no charge from the author, Steven L. Shafer, MD, Anesthesiology Service (112A), Pavamc, 3801 Miranda Ave, Palo Alto, CA 94304, or from the WWW at URL: http:@pkpd.icon.palo-alto.med.va.gov.). Stanpump attempts to maintain a constant plasma concentration by simulation. The programmed pump variables do not consider any stereoselective differences in ketamine pharmacokinetics. Pseudo-steady-state concentrations of 350 ng ml^{-1} and 180 ng ml^{-1} were targeted for racemic and ketamine (S+), respectively.

GENERAL CONDITION AND SIDE EFFECTS

Before the tests, subjects were asked if they felt calm/agitated (0 = very calm, 10 = very agitated), well/bad (0 = very well, 10 = very bad), and had side effects such as dreams (0 = no dreams, 10 = dreams all the time), and if dreams (0 = very pleasant dreams, 10 = very unpleasant dreams), or hallucinations (0 = none, 10 = much). The general condition and side effects were rated on a 10-cm electronic rating scale. Dreams were explained as experiences having a connection to reality and hallucinations without connection to reality.

STUDY DESIGN

All subjects attended three times, each attendance separated by 1 week.

Each time a trial test series was performed before recording of a baseline test series.

A test series lasted approximately 20–25 min and included recording of the following:

- Side effect rating
- Reaction time
- Skin temperature
- Heat pain detection threshold to 314 and 1570 mm^2 (8 °C s^{-1}, 2 s duration at peak temperature)
- VAS rating to 50°C at 314 and 1570 mm^2 (8°C s^{-1}, 2 s duration at 50 °C)
- VAS rating to 50°C at 314 mm^2 (2°C s^{-1}, 8°C s^{-1})
- Heat summation pain threshold (0.66 Hz, 30 °C s^{-1}, 314 mm^2)
- Electrical summation pain threshold (2 Hz)
- VAS rating to 1.2 × the initial electrical pain summation threshold
- Pressure pain detection and tolerance thresholds (28 and 92 mm^2)

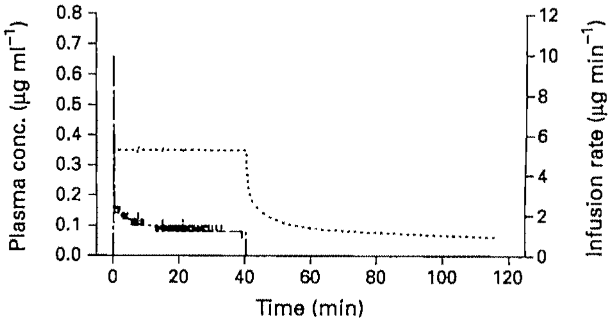

Figure 2 Infusion rates used by the "Stanpump" to obtain the estimated target plasma concentration (dotted line) of 350 ng ml^{-1} for ketamine (racemic).

After the baseline series the target-controlled infusion was started and equilibration for 15 min was allowed to ensure constant plasma and CNS concentrations (fig. 2). A test series was then performed. Thereafter, the infusion was stopped, and a final test series was performed 60 min after the infusion was terminated. At this last test series the predicted plasma concentration (Stanpump) declined to only 6–8 ng ml^{-1} for racemic ketamine and 3–4 ng ml^{-1} for ketamine S+.

STATISTICAL ANALYSIS

For each measurement (temperature, heat, pain threshold, etc.), the variance between drugs (racemic ketamine, (S+)-ketamine, placebo) and the conditions (before, during and after infusion) were tested using a two-factor ANOVA for repeated measures. In the event of interaction between drug and condition, multiple pairwise comparisons of the measures (e.g. heat, pain threshold before *vs* after ketamine) were performed with the Student–Newman–Keuls method for corrections of repeated measures. In cases where data for different measurements (e.g. small and large stimulation areas) were pooled, Student's *t* test was used for comparison. $P < 0.05$ was regarded as significant.

Results

GENERAL CONDITION AND SIDE EFFECTS

One volunteer was able to participate in only two of the sessions and was withdrawn from the rest of the experiment. During the three sessions, no differences in "general feelings" (table 1) were reported before, during or after infusion. The amounts of infused ketamine (racemic) and ketamine (S+) were 59.75 (5.29) mg and 29.22 (2.55) mg, respectively.

The reaction times (table 2) to auditory stimuli were increased ($P < 0.001$–0.002) by approximately 100 and 50 ms after infusion of ketamine (racemic) and ketamine (S+), respectively. These changes were significant ($P < 0.001$–0.003) compared with placebo. Ketamine (racemic) showed a significantly

Table 1 General feeling (feeling calm/agitated, feeling well/bad) and side effects (dreams and hallucinations) were rated on a 10-cm VAS scale (mean values are given), 20 min after administration of ketamine (ket) (racemic)/ketamine (S+)/placebo (Pla)

Condition	VAS (cm) Ket/Ket (S+)/Pla
Feeling	
Calm(0)/agitated (10)	
Before	0.4/0.8/0.8
During	1.2/0.9/0.2
After	0.2/0.3/0.2
Well (0)/bad (10)	
Before	0.7/0.3/0.2
During	0.7/0.8/0.2
After	0.7/0.6/0.2
Side effects	
Dreams (0–10)	1.8/2.1/0
Dreams	
Pleasant (0)/unpleasant (10)	0.7/1.1/0
Hallucinations (0–10)	2.1/1.2/0

Table 2 Mean (SD) skin temperature and reaction time measured before, during and after ketamine (racemic)/ketamine (S+)/placebo infusions. *Different from baseline; †different from placebo; ‡difference between drugs

Measurements	Ketamine	Ketamine (S+)	Placebo
Skin temperature (°C)			
Before	32.1 (0.9)	32.0 (1.0)	32.2 (1.3)
During	31.4 (1.0)*†	31.4 (1.1)*†	32.1 (1.8)
After	32.8 (0.9)	32.7 (1.2)	32.5 (1.4)
Reaction time (ms)			
Before	102 (29)	105 (28)†	105 (22)
During	200 (82)*†‡	150 (54)*	100 (20)
After	114 (44)	110 (40)	101 (25)

prolonged reaction time ($P < 0.02$) compared with ketamine (S+).

The approximately 0.1-s increase in reaction time for ketamine affected the thresholds only marginally. The slowing in reaction time caused maximally a 5-kPa increase in pressure thresholds, and 0.2 °C and 0.8 °C increases in thresholds to slow and fast temperature rise times. As skin temperature at the same time was decreased by approximately 1 °C, the influence was limited.

Table 3 Mean (SD) pressure pain detection and tolerance pain thresholds measured before, during and after ketamine (racemic)/ketamine (S+)/placebo infusions. Small (28 mm^2) and large (92 mm^2) areas were used. *Different from baseline; †different from placebo; ‡difference between drugs

Measurements	Ketamine	Ketamine (S+)	Placebo
Detection threshold (small, kPa)			
Before	683 (75)	650 (63)	732 (85)
During	1057 (109)*†	965 (110)*†	703 (78)
After	657 (78)	584 (63)	696 (101)
Tolerance threshold (small, kPa)			
Before	1327 (114)	1360 (137)	1310 (127)
During	1491 (153)*	1567 (137)*†	1340 (119)
After	1261 (96)	1324 (129)	1209 (117)
Detection threshold (large, kPa)			
Before	371 (121)	336 (142)	410 (134)
During	615 (172)*†‡	482 (153)*†	435 (119)
After	377 (82)	332 (79)	388 (101)
Tolerance threshold (large, kPa)			
Before	849 (177)	831 (239)	815 (242)
During	978 (231)*†	935 (207)*	819 (243)
After	753 (179)	779 (206)	768 (207)

PRESSURE PAIN DETECTION AND TOLERANCE THRESHOLDS (TABLE 3)

For the small probe (28 mm^2), increases ($P <$ 0.006–0.004) in pain detection and pain tolerance thresholds were obtained after infusion of ketamine (racemic) (374 and 164 kPa) and ketamine (S+) (315 and 207 kPa).

For the large probe (92 mm^2), increases ($P <$ 0.002–0.008) in pain detection and pain tolerance thresholds were obtained after infusion of ketamine (racemic) (244 and 129 kPa) and ketamine (S+) (146 and 104 kPa). A difference ($P <$ 0.002–0.03) from placebo was found for all tolerance thresholds except for the ketamine (S+) tolerance threshold. An increase ($P < 0.01$) in the pain detection threshold was found after infusion of ketamine (racemic) compared with infusion of ketamine (S+).

The active drugs affected the large area to the same degree as the small area. When threshold determinations for the small and large probes were pooled, the pain detection thresholds increased ($P < 0.004$) more than the tolerance thresholds for both drugs.

HEAT PAIN DETECTION THRESHOLDS TO ONE AND FIVE THERMODES (TABLE 4)

For one thermode (314 mm^2), an increase in heat pain threshold (2.7 °C) was obtained after infusion of ketamine (racemic) ($P < 0.001$) and ketamine (S+) ($P < 0.004$, 2.1 °C). These changes were significant compared with placebo ($P < 0.002$, $P < 0.003$). For simultaneous activation of five thermodes (1570 mm^2), increases ($P <$ 0.001–0.002) in the thresholds after ketamine (racemic) (3.6 °C) and ketamine (S+) (2.4 °C) were found compared with baseline and placebo, respectively. No differences were found between threshold changes for one and five thermodes. When threshold determinations for both drugs were pooled, a trend ($P > 0.08$) towards a larger increase in the five probe threshold than in the one probe threshold was found. Infusion of ketamine (racemic) increased significantly the threshold to five probes ($P < 0.002$) more than ketamine (S+).

VAS RATING TO ONE AND FIVE THERMODES (TABLE 4)

A decrease in the VAS ratings to one thermode (50 °C, 8 °C s^{-1}, 2 s duration) was found after infusion of ketamine (racemic) and ketamine (S+) compared with baseline ($P <$ 0.001–0.002) and placebo ($P <$ 0.01–0.02), showing no difference between drugs.

A decrease in VAS ratings to five thermodes (50 °C, 8 °C s^{-1}, 2 s duration) was found after infusion of ketamine (racemic) and ketamine (S+) compared with baseline ($P <$ 0.001–0.003) and placebo ($P <$ 0.001–0.006), with no difference between drugs. There were no differences between VAS rating changes for one and five thermodes. If the heat pain thresholds and the VAS ratings to one and five thermodes for the two drugs were pooled statistically, measurements related to the five probe stimulation were changed significantly ($P < 0.02$) more than the one probe measurement.

Table 4 Mean (SD) variables measured before, during and after ketamine (racemic)/ketamine (S+)/placebo infusions. *Different from baseline; †different from placebo; ‡difference between drugs

Measurements	Ketamine	Ketamine (S+)	Placebo
Electrical summation threshold (mA)			
Before	6.3 (1.8)	6.1 (2.4)	6.6 (1.8)
During	7.7 (1.9)*†	7.3 (2.6)*†	6.7 (1.7)
After	7.0 (1.9)	6.6 (2.6)	6.9 (1.9)
VAS 1.2x summation threshold (cm)			
Before	4.8 (1.9)	5.1 (2.4)	4.9 (1.9)
During	2.6 (1.2)*†	3.7 (2.9)*†	4.8 (2.3)
After	3.8 (1.7)	4.5 (1.8)	4.3 (2.3)
Heat summation threshold (°C) ($30\,°C\ s^{-1}$, 1 probe)			
Before	47.7 (1.0)	48.0 (0.7)	48.0 (1.2)
During	50.6 (1.6)*†	49.9 (1.6)*†	47.8 (1.2)
After	47.8 (1.2)	48.0 (0.9)	47.8 (1.6)
Heat threshold (°C) ($8\,°C\ s^{-1}$, 2 s duration, 1 probe)			
Before	46.6 (1.2)	47.2 (1.4)	46.7 (1.7)
During	49.3 (1.5)*†	49.3 (2.0)*†	46.9 (1.7)
After	47.2 (1.1)	47.2 (1.4)	46.8 (2.1)
Heat threshold (°C) ($8\,°C\ s^{-1}$, 2 s duration, 5 probes)			
Before	44.9 (0.9)	44.8 (1.9)	44.4 (2.2)
During	48.5 (1.3)*†‡	47.2 (1.7)*†	45.0 (2.3)
After	45.6 (1.0)	45.5 (1.4)	45.1 (2.3)
VAS 50 °C (cm) ($8\,°C\ s^{-1}$, 2 s duration, 1 probe)			
Before	4.8 (2.0)	3.9 (2.1)	4.3 (2.2)
During	2.7 (2.3)*†	2.2 (2.6)*†	4.2 (2.4)
After	4.5 (2.1)	3.6 (2.4)	4.0 (2.8)
VAS 50 °C (cm) ($8\,°C\ s^{-1}$, 2 s duration, 5 probes)			
Before	6.1 (2.1)	6.0 (1.8)	6.2 (1.6)
During	3.8 (2.6)*†	4.1 (2.7)*†	6.2 (1.9)
After	6.1 (1.8)	6.1 (2.1)	6.2 (2.0)
VAS 50 °C (cm) ($2\,°C\ s^{-1}$, 1 probe)			
Before	4.6 (2.0)	4.2 (1.8)	4.6 (2.1)
During	2.7 (2.6)*†	1.9 (1.4)*†	4.2 (2.6)
After	4.8 (1.7)	4.3 (2.2)	4.4 (2.5)
VAS 50 °C (cm) ($8\,°C\ s^{-1}$, 1 probe)			
Before	2.5 (2.0)	2.1 (1.5)	2.7 (2.0)
During	0.7 (0.8)*†	1.0 (1.0)*†	2.9 (2.2)
After	3.1 (2.2)	2.8 (2.2)	2.6 (2.5)

VAS RATING TO ONE THERMODE USING DIFFERENT RISE TIMES (TABLE 4)

A decrease in VAS ratings to one thermode (50 °C, $2\,°C\ s^{-1}$) was found after infusions of ketamine (racemic) and ketamine (S+) compared with baseline ($P < 0.001$–0.002) and placebo ($P < 0.008$–0.01), with no difference between drugs.

A decrease in VAS ratings to one thermodes (50 °C, $8\,°C\ s^{-1}$) was found after infusions of ketamine (racemic) and ketamine (S+) compared with baseline ($P < 0.002$–0.006) and placebo ($P < 0.001$–0.008), with no difference active drugs.

A similar effect of the thresholds to $2\,°C\ s^{-1}$ and $8\,°C\ s^{-1}$ was found for the drugs.

VAS RATING TO ONE THERMODE USING DIFFERENT DURATIONS (TABLE 4)

The VAS rating to one thermode (50 °C and $8\,°C\ s^{-1}$) was compared between the session where the temperature decrease immediately after 50 °C was reached (0 s duration), and the session where temperature was maintained at 50 °C for 2 s (2-s duration). The VAS score of the long duration stimulus was approximately two times higher than the VAS score of the short stimulus, but the changes provoked by the drugs were not different.

When data from both drug studies were pooled, VAS of the stimuli of long duration (50°, $2\,°C\ s^{-1}$, 2 s duration) was changed significantly ($P < 0.004$) more than for the stimuli of short duration (50°, $8\,°C\ s^{-1}$ threshold, 0 s duration).

HEAT SUMMATION PAIN THRESHOLD (TABLE 4)

Increases in the summation threshold were found after infusion of ketamine (racemic) ($P < 0.001$, 2.9 °C) and ketamine (S+) ($P < 0.001$, 1.9 °C), and these increases were significant compared with placebo ($P < 0.001$, $P < 0.001$, respectively).

ELECTRICAL SUMMATION PAIN THRESHOLD (TABLE 4)

Increases in the summation threshold were found after infusion of ketamine (racemic) ($P < 0.003$, 1.4 mA) and ketamine (S+) ($P < 0.003$, 1.2 mA), and these increases were significant compared with placebo ($P < 0.005$).

VAS RATING TO REPEATED ELECTRICAL STIMULI (TABLE 4)

The VAS ratings to repeated, electrical stimuli were reduced by ketamine (racemic) ($P < 0.002$) and ketamine (S+) ($P < 0.02$) and these decreases were significant compared with placebo ($P < 0.004$–0.04).

Discussion

Our study suggests that ketamine (racemic) and ketamine (S+) had potent analgesic effects compared with placebo on various pain modalities involving spatial and temporal summation aspects. No systematic differences in the analgesic effect of ketamine (racemic) and ketamine (S+) on summation were detected, indicating a potency for the (S+)-isomer of twice that of the racemic mixture. Both drugs attenuated repeated heat and electrical stimuli, pain from large areas more than pain evoked from small areas, and long duration heat stimuli more than short duration stimuli. Ketamine (racemic) prolonged the reaction time significantly more than ketamine (S+) indicating a different degree of sedation or impairment of motor performance.

KETAMINE (RACEMIC) *VS* KETAMINE (S+)

A dose ratio (1:2) has been found using depression of the auditory evoked potentials[18] or the hypnotic effect[19] as variables. These studies did not evaluate analgesic effects. Our study suggests that the chosen target concentration (assumed to be close to actual plasma concentrations) of ketamine (S+) of 180 ng ml^{-1} inhibited central summation equally as 350 ng ml^{-1} of ketamine (racemic). However, true potency comparisons require dose–response curves for both the racemic mixture and the (S+)-isomer. In a recent clinical study the (S+)-isomer was found to be four times more potent than the (R−)-isomer for management of postoperative orofacial pain.[16]

NMDA antagonists are reported to prevent wind-up in a wide dynamic range of neurones as a result of long-lasting C-fibre stimulation.[12 13 20] Interestingly, these drugs do not reduce the response to short-lasting C-fibre stimulation.[12] For the management of acute pain states possibly inducing wind-up and hyperexcitability (e.g. trauma and surgical procedures), ketamine (S+) seems to be a suitable drug for further clinical study.

TEMPORAL SUMMATION

For a long time temporal summation has been considered as an important mechanism for pathophysiological pain.[6 7] We have recently shown that extradurally administered analgesics (bupivacaine) have substantially less effect on stimuli with long duration than on stimuli with short duration.[4 5] This indicated that temporal summation may be an important factor for the lack of effectiveness of such anaesthetic procedures. During general anaesthesia with isoflurane, repeated stimuli were found to be largely unaffected compared with single stimuli.[3]

In this study, ketamine affected repeated stimuli and thermal stimuli of long duration similar to or more than stimuli of short duration. This was interpreted as modulation of the facilitatory mechanisms underlying central temporal summation.

SPATIAL SUMMATION

It has been reported that spinally and extradurally administered analgesics have much less effect on stimuli covering large areas than on localized stimuli.[1 2 4] The threshold to large area stimulation was lower than that to small area stimulation, indicating the role of spatial summation as described previously.[21] The measurements from the large areas were affected to the same degree or even more by ketamine than the small areas, indicating possible reduction by ketamine of the facilitatory mechanism underlying spatial summation. The obvious, complementary efficacy profiles between traditional anaesthetic procedures and ketamine suggest a clinical advantage of combining the two synergetic effects: generalized analgesia together with inhibition of summation.

EFFECT OF KETAMINE ON HEAT AND PRESSURE THRESHOLDS

The increase in heat pain threshold in this study contrasts with the results of Anis and co-workers[22] who found that ketamine had no consistent effect on the responses of dorsal horn neurones to natural stimuli, and to human findings.[23] In the study of Kristensen, Svensson and Gordth,[23] no effect of CPP (a NMDA receptor antagonist) on the thermal pain detection threshold was detected. We have recent evidence that high intensity laser heat pulses and brief electrical (20 ms train) pulses were not affected by ketamine (racemic).[14]

In this study the detection pressure threshold was increased by ketamine more than the tolerance threshold. Animal studies have indicated that the effect of ketamine is dependent on stimulus intensity.[24]

From an "inhibition of temporal summation" point of view, the pressure pain thresholds to small area stimulation should be inhibited more than the thresholds to the large area as the pressure pain thresholds are largest for the small area and hence it takes more time to reach the small area thresholds. From an "inhibition of spatial summation" point of view, the pressure pain thresholds to small area stimulation should be inhibited less than the thresholds to large areas. Therefore, this suggested that ketamine should provoke the largest changes in the pressure pain detection threshold to small area, and pressure pain tolerance threshold to large areas should be affected less. This was the result as seen in table 3 (mean changes of 344 kPa *vs* 116 kPa; $P < 0.001$).

In summary, we found that both ketamine (racemic) and ketamine (S+) had a general analgesic effect, an effect on repeated stimuli, an effect on long duration stimuli and an effect on stimuli covering large areas. The (S+)-isomer was approximately twice as potent in inhibiting central summation as the racemic mixture of ketamine at the chosen target concentrations. The chosen doses had the same number of side effects, although these were minimal.

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References

1. Arendt-Nielsen L, Øberg B, Bjerring P. Quantitative assessment of extradural bupivacaine analgesia. *British Journal of Anaesthesia* 1990; **65**: 633–638.
2. Arendt-Nielsen L, Anker-Møller E, Bjerring P, Spangsberg N. Onset phase of spinal bupivacaine analgesia assessed quantitatively by laser stimulation. *British Journal of Anaesthesia* 1990; **65**: 639–642.
3. Petersen-Felix S, Arendt-Nielsen L, Bak P, Fischer M, Bjerring P, Zbinden AM. The effect of isoflurane on repeated nociceptive stimuli (central temporal summation). *Pain* 1996; **64**: 277–281.
4. Brennum J, Arendt-Nielsen L, Secher NH, Jensen TS, Bjerring P. Quantitative sensory examination in human epidural anaesthesia and analgesia in man; effect of lidocaine. *Pain* 1992; **52**: 27–34.
5. Brennum J, Nielsen PT, Horn A, Arendt-Nielsen L, Secher NH. Quantitative sensory examination in human epidural anaesthesia and analgesia in man; dose–response effect of bupivacaine. *Pain* 1994; **56**: 315–326.
6. Noordenbos W. *Pain*. Amsterdam: Elsevier, 1959.
7. Dubner R, Sharav Y, Gracely RH, Price DD. Idiopatic trigeminal neuralgia. Sensory features and pain mechanisms. *Pain* 1987; **31**: 23–33.
8. Dubner R. Pain and hyperalgesia following tissue injury. New mechanisms and new treatments. *Pain* 1991; **44**: 213–214.
9. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first and central summation of second pain evoked by noxious heat pulses. *Pain* 1977; **3**: 57–68.

10. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994; **59**: 165–174.
11. Arendt-Nielsen L, Brennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *European Journal of Applied Physiology* 1994; **68**: 266–273.
12. Davies SN, Lodge D. Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurons in the dorsal horn of the rat. *Brain Research* 1987; **424**: 402–406.
13. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; **44**: 293–299.
14. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P. The effect of NMDA-antagonist (ketamine) on central temporal summation—a double-blind placebo-controlled experimental human study. *Anesthesia and Analgesia* 1995; **81**: 63–68.
15. Marietta MP, White PF, Pudwill CR, Way WL, Trevor AJ. Biodisposition of ketamine in the rat. Self-induction of metabolism. *Journal of Pharmacology and Experimental Therapeutics* 1977; **196**: 536–544.
16. Mathisen LC, Skjelbred P, Skoglund LA, Øye I. Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. *Pain* 1995; **61**: 215–220.
17. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, Zsigmond EK. Ketamine kinetics in unmedicated and diazepam-premedicated subjects. *Clinical Pharmacology and Therapeutics* 1984; **36**: 645–653.
18. Schwender D, Faber-Züllig E, Fett W, Klasing S, Finsterer U, Pöppel E, Peter K. Mid-latency auditory evoked potentials in humans during anesthesia with S(+) ketamine—a double-blind, randomized comparison with racemic ketamine. *Anesthesia and Analgesia* 1994; **78**: 267–274.
19. Doenicke A, Angster R, Mayer M, Adams HA, Grillenberger G, Nebauer AE. Die wirkung von S(+)-ketamin auf katecholamine und cortisol im serum. *Anaesthesist* 1992; **41**: 597–603.
20. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurons following C-fibre stimulation. *Neuropharmacology* 1987; **26**: 1235–1238.
21. Price DD, McHaffie JG, Larson MA. Spatial summation of heat-induced pain. Influence of stimulus area and spatial separation of stimuli on perceived pain sensation intensity and unpleasantness. *Journal of Neurophysiology* 1989; **62**: 1270–1279.
22. Anis NA, Headley PM, Lodge D, West D. Lack of involvement of N-methyl-aspartate receptors in segmental synaptic excitation of cat lumbar dorsal horn neurones. Studies with ketamine. *Journal of Physiology (London)* 1985; **328**: 10P.
23. Kristensen JD, Svensson B, Gordth TJR. The NMDA-receptor antagonist CPP abolishes neuropathic "wind-up pain" after intrathecal administration in humans. *Pain* 1992; 51: 249–253.
24. Conseiller C, Benoist JM, Hamann KF, Maillard MC, Besson JM. Effects of ketamine (CI581) on cell responses to cutaneous stimulations in laminae IV and V in the cat's dorsal horn. *European Journal of Pharmacology* 1972; **18**: 346–352.

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Normal saline i.v. fluid load decreases uterine activity in active labour

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Summary

This study was designed to observe the effects of i.v. fluid infusion on uterine activity during normal labour in women receiving an extradural block. Thirty-four women in spontaneous labour at term gestation were allocated randomly and prospectively to one of three i.v. pre-extradural fluid load groups: group A, no fluid load; group B, normal saline 500 ml; and group C, normal saline 1000 ml. Continuous internal measurement of uterine activity was observed before, during and after fluid infusion and extradural block. In groups A and B, uterine activity did not change. In group C, uterine activity decreased after infusion of saline ($P < 0.01$) and returned to baseline over the next 20 min. Extradural block was not associated with a change in uterine activity. Hypotension was not increased in the group that received no fluid preload. (*Br. J. Anaesth.* 1996; **77**: 632–635)

Key words
Fluids, i.v. Anaesthetic techniques, extradural. Uterus, activity.

There is disagreement on the effect of lumbar extradural block on uterine activity and its influence on the progress of labour.[1–5] It is presently common obstetric practice in the USA to infuse 500–1000 ml of i.v. normal saline as initial treatment in the tocolytic therapy of preterm labour.[6] The purpose of this study originated from the question: if an i.v. fluid load of normal saline 500–1000 ml effectively inhibits uterine activity in more than 50% of subjects in preterm labour, what is the effect of similar fluid load during normal active labour? If uterine activity is inhibited by such a fluid load, could this explain observations of decreased uterine activity after extradural block, a procedure normally preceded by an i.v. fluid load? This study was designed to observe the individual effects of i.v. fluid load and extradural block on uterine activity during normal active labour.

Patients and methods

After obtaining approval from the Institutional Committee for Human Studies and informed consent, we studied 34 healthy, ASA I–II term parturients in spontaneous labour. Patients were allocated randomly and prospectively to one of three pre-extradural i.v. fluid load groups: group A, no fluid load; group B, normal saline 500 ml infused over 10 min; group C, normal saline 1000 ml infused over 10 min. All subjects received maintenance i.v. fluids: 5% glucose 125 ml h^{-1} in 1/2 normal saline from admission to the labour ward to just before the time of study (mean = 550 ml). None of the subjects received any medication before the study. Both primiparae and multiparae were studied. Extradural analgesia was performed with the subject in the lateral position with a total of 12 ml of 0.25% bupivacaine without adrenaline (a 3-ml test dose followed by 9 ml). After insertion of the extradural, continuous uterine displacement with a right hip wedge was maintained throughout the study. Fetal heart rate and maternal arterial pressure were noted at 5-min intervals and treatment for maternal hypotension was recorded. Maternal arterial pressure was determined at 1-min intervals for 5 min and at 5-min intervals thereafter for the first 30 min after local anaesthetic injection. If maternal arterial pressure decreased to less than 100 mm Hg for more than 1–2 min, i.v. ephedrine was given in 5-mg increments to obtain an arterial pressure of >100 mm Hg.

Continuous internal measurement of uterine activity was divided into 7–10-min intervals: 10 min of baseline uterine activity, 10 min of fluid infusion, 20 min (2 × 10 min) for recovery from possible fluid load effects, and for 30 min after extradural injection. Measurements were continuous after both fluid load and extradural injection, with 10 min allowed between measurements for insertion of the extradural catheter. Intrauterine pressure was measured with catheters positioned by an obstetrician in the uterine cavity. These were placed electively for the purpose of the study and not for obstetric indications. Quantitative measurement of

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uterine activity units, frequency, duration and intensity of contractions were calculated from the area under the graphic curve produced on tracing paper from the fetal heart monitor (Corometrics). Calculation of uterine activity for each interval was made by the same obstetrician (P. S.) who was unaware of the amount of fluid load or the time of extradural injection. One uterine activity unit is equivalent to 50 mm Hg s^{-1}.[7]

Two subjects were excluded in group A because precipitous delivery occurred before extradural block was performed. One subject each from groups B and C received fluid load measurements but rapidly progressed to delivery before extradural block could be accomplished. Constraints during the measurement period included avoidance of change in subject position, voluntary pushing or intrauterine pressure system flushing. Measurements were not made if the subject vomited, in the presence of asymmetric tracing or if there was a suspicion of system malfunction. Cervical dilatation at the time of measurements was 4–6 cm.

Statistical analysis included paired Student's t test for patient variables. Analysis of variance over time within and between groups was determined for uterine activity with Tukey's test because of the number of subjects involved.

Results

There were no differences between groups in maternal age, height, weight, gestational age or cervical dilatation at the start of the study (table 1).

In group A (maintenance fluid only), uterine activity did not change during any period. In group B (fluid infusion of 500 ml i.v.), there was a decrease in uterine activity after the infusion, but this was not significant. In group C (infusion of 1000 ml i.v.), uterine activity decreased after the infusion ($P < 0.01$) but returned to baseline over the next 20 min. Mean uterine activity did not decrease in any group after induction of extradural block. Uterine activity in the three groups in response to fluid load and extradural block is summarized in figure 1. There were no differences between groups in changes in maternal arterial pressure and there were no abnormal changes in fetal heart rate during the study. Duration of labour was not different between groups after initiation of the study.

There were no differences in incidence and severity of hypotension between the groups.

Discussion

Several factors associated with extradural block are reported to decrease uterine activity, including inadvertent aorto-caval compression, maternal hypotension, β agonist activity from low-dose adrenaline in the local anaesthetic solution, and possible direct local anaesthetic effects on the myometrium. After controlling for these variables, our data indicated that an i.v. fluid load before regional block caused a transient decrease in uterine activity.

Rout and co-workers have reported attenuated protection against hypotension with pre-spinal i.v.

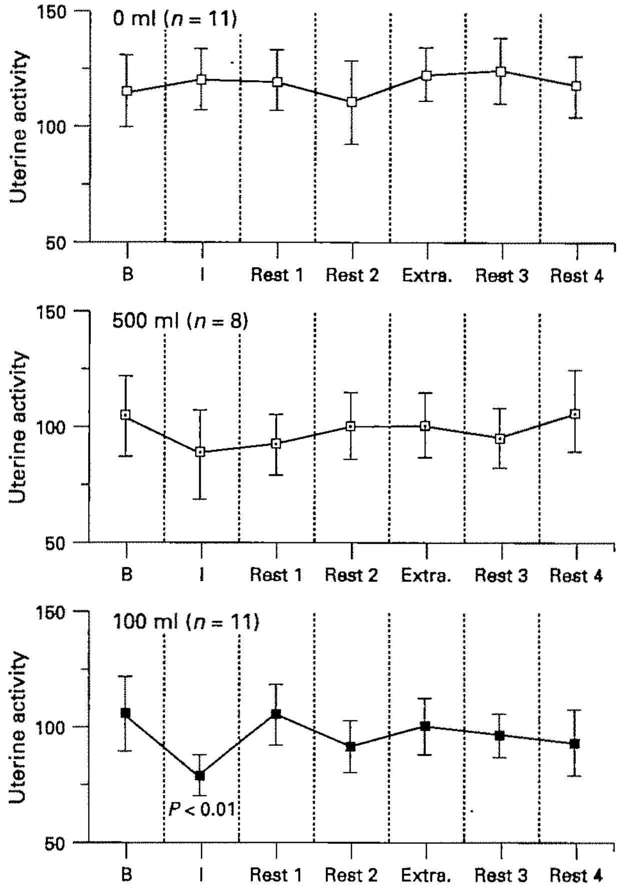

Figure 1 Uterine activity (mean, SD) after no fluid preload (0 ml) and after i.v. infusion of 500 and 1000 ml. B = Baseline, I = infusion, Extra. = extradural injection.

Table 1 Patient characteristics (mean (SD or range)) or number

	Group A (no preload)	Group B (500 ml)	Group C (1000 ml)
n	11	8	11
Age (yr)	20.7 (16–31)	22.7 (18–33)	21.1 (16–29)
Gestational age (weeks)	39.5 (38–40)	39 (37–40)	39 (38–40)
Weight (kg)	76.4 (6)	79.7 (6.5)	75.5 (9.5)
Height (cm)	64.7 (0.7)	65.3 (0.5)	62.8 (1.8)
Nullipara	8	5	7
Multipara	3	3	4
Cervical dilatation at study (cm)	5 (0.3)	4 (0.3)	4 (0.4)
I.v. fluids before study (ml h^{-1})	125	125	125
Forceps	3/11	2/8	3/11
Vaginal delivery	9/11	7/8	9/11
Caesarean delivery	2/11	1/8	2/1

fluid loading during Caesarean section.[8] On a smaller scale we found that subjects who received no fluid load had no greater incidence or severity of hypotension after 0.25% bupivacaine 12 ml than subjects who received 1000 ml i.v. fluid preload. It may be that as all subjects received maintenance i.v. fluids, intravascular volume was adequate to compensate for the increased vascular capacitance associated with a T9 (mean) sympathectomy. Our data suggest that a fluid load of 1 litre i.v. did not decrease the incidence of maternal hypotension in labouring patients.

The incidence of slowing or arrest of labour, as defined by failure of cervical dilatation in the absence of extradural block, was reported by Bottoms, Sokol and Rosen as approximately 20%, with 5.5% defined as secondary arrest requiring obstetric intervention.[9] Arrest or slowing of labour was associated most commonly with decreased uterine activity. This indicates that under normal conditions one of five parturients experiences decreased uterine activity during labour, independent of external medication.

The effect of extradural block on labour and uterine activity has been debated almost from the beginning of its use in obstetrics. Unfortunately, the clinical evidence offered in these arguments is largely anecdotal, uncontrolled, non-randomized and usually retrospective. Friedman and Sachtleben, in 1959, reported that caudal block to T10 did not alter uterine activity but that higher levels of block were associated with longer labours.[10] This report was not based on a prospective, randomized series and maternal position or arterial pressure after caudal block was not reported. Lowensohn and colleagues prospectively studied the effect of extradural lignocaine and propitocaine (a drug no longer in use) and reported a decrease in uterine activity after each injection of lignocaine that lasted approximately 20 min.[1] This study was flawed by the addition of adrenaline to the local anaesthetic injectate, and neither the amount of preblock fluid loading nor the assurance of uterine displacement were reported.

Quantitation of uterine activity during labour cannot be done with external tocodynamometry. Accurate measurement requires intra-cavitary placement of either a transducer or a fluid-filled catheter with a pressure transducer connected to a fetal monitor where the signal is expressed as a continuous tracing calibrated in mm Hg. Earlier investigators estimated uterine activity in Montevideo units where peak height of the contraction was multiplied by the number of contractions.[11] Hon and Paul described a more precise method for quantitation of uterine activity measurement in which the integral under the uterine contraction curve was calculated and expressed in "torr seconds".[7] In this study, uterine activity was estimated by directly measuring the area under the uterine contraction curve and above baseline tone.

Despite strict adherence to uterine displacement, avoidance of maternal hypotension and pre-block i.v. fluid load, transient decreases in uterine activity are still observed occasionally after extradural block for analgesia in labour. Normal uterine activity requires a complex interplay between ongoing uterine smooth muscle biochemical changes and a set of external maternal and fetal signals.[12] These external signals may be neural, or hormonal; the uterine smooth muscle and vascular system are innervated by sympathetic and peptidergic fibres and their transmitter and receptor content changes during pregnancy. Our data suggest that prehydration before extradural block attenuated uterine activity. There are several possible explanations for decreased uterine activity observed after a fluid load. Valenzuela, Cline and Hayashi speculated that oxytocin and vasopressin secretion are inhibited directly at the neurohypophysis.[6] Transient dilution of plasma oxytocin concentrations by a fluid load may temporarily attenuate uterine activity. Both of these suggestions are in dispute because the effect of oxytocin on uterine activity is no longer thought to be dependent on circulating oxytocin concentrations but related rather to the number of myometrial oxytocin receptors and their degree of activity.[12] Another suggestion is that the temperature (~22 °C) of the infused i.v. solution may affect uterine activity. This is unlikely because cooling of the blood by 1 litre of room temperature saline would be both small and rapidly dissipated.

Rapid volume expansion increases transmural atrial distending pressure. This stimulates vagal neural afferents which may decrease posterior pituitary hormone secretion and sympathetic (particularly renal) nerve activity, and perhaps efferent peptidergic nerve activity. We speculate that the mechanism may lie either in a sudden humoral release, such as atrial natriuretic peptide (ANP) after rapid atrial distension, or a direct mechanical effect on the uterine vasculature producing local release of endothelial vasoactive peptides. Bek, Ottesen and Fahrenkrug have shown ANP to be a potent inhibitor of rat uterine smooth muscle contraction.[13]

Recently Eledjam and co-workers reported a 172% increase in ANP plasma concentrations of labouring women 15 min after i.v. fluid challenge with dextran 40 250 ml.[14] ANP is a 28 amino acid peptide which is secreted directly by the atrium into the coronary veins, and causes vasodilatation, natriuresis and diuresis, and inhibition of secretion or end-organ effects of several vasoactive hormones, including angiotensin II and noradrenaline.[15] Concentrations of ANP increase slightly during pregnancy, and increase further with volume loading.[14] In contrast, Grunewald and colleagues infused 0.9% Ringer's lactate 15 ml kg^{-1} in normal parturients over 30 min. This caused a decrease in ANP from 6.5 to 4.6 pmol $litre^{-1}$.[16] This may indicate that different i.v. infusates have different effects on ANP concentrations. ANP receptors are present in the non-pregnant rat uterus and inhibit uterine contraction and blood flow.[14 17] The time course of ANP release and action is consistent with the role of ANP in decreasing uterine activity during volume loading. However, the overall role of ANP in parturition is unknown.

References

1. Lowensohn RI, Paul RH, Fales S, Yeh SY, Hon EH. Intrapartum epidural anesthesia, an evaluation of effects on uterine activity. *Obstetrics and Gynecology* 1974; 44: 388–393.

2. Willdeck-Lund G, Lindmark G, Nilsson BA. Effect of segmental epidural analgesia upon the uterine activity with special reference to the use of different local anaesthetic agents. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 519–528.
3. DeVore JS, Eisler EA. Effects of anesthesia on uterine activity. In: Shnider SM, Levinson G, eds. *Anesthesia for Obstetrics*. Baltimore: Williams and Wilkins, 1987; 41–48.
4. Morgan BM. Problems of analgesia in labour. In: Morgan B, ed. *Problems in Obstetric Anaesthesia*. New York: Wiley and Sons, 1987; 166–170.
5. Ferguson JE, Allbright GA III. Physiology of labor. In: Allbright GA III, Ferguson JE II, Joyce TH III, Stevenson DK, eds. *Anesthesia in Obstetrics*. Boston: Butterworths, 1986; 87–90.
6. Valenzuela G, Cline S, Hayashi RH. Follow-up of hydration and sedation in the pretherapy of premature labor. *American Journal of Obstetrics and Gynecology* 1983; **147**: 396–398.
7. Hon EH, Paul RH. Quantitation of uterine activity. *Obstetrics and Gynecology* 1973; **42**: 368–370.
8. Rout CC, Akoojee SS, Rocke DA, Gouws E. Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1992; **68**: 394–397.
9. Bottoms SF, Sokol RJ, Rosen MG. Short arrest of cervical dilatation: A risk for maternal/fetal/infant morbidity. *American Journal of Obstetrics and Gynecology* 1981; **140**:108–116.
10. Friedman EA, Sachtleben MR. Caudal anesthesia. The factors that influence its effects on labor. *Obstetrics and Gynecology* 1959; **13**: 442–450.
11. Caldeyro Barcia R, Alvarez H. Abnormal uterine action in labour. *Journal of Obstetrics and Gynaecology of the British Empire* 1952; **59**: 646.
12. Carsten ME, Miller JD. A new look at uterine muscle contraction. *American Journal of Obstetrics and Gynecology* 1987; **157**: 1303–1315.
13. Bek T, Ottesen B, Fahrenkrug J. The effect of gallanin, CGRP and ANP on spontaneous smooth muscle activity of rat uterus. *Peptides* 1988; **9**: 497–500.
14. Eledjam JJ, Thomas H, Macheboeuf M, Baudin G, Ferrer JM, d'Athis F. Influence of vascular loading on the secretion of the atrial natriuretic factor during epidural analgesia for labor. *Anesthesiology* 1989; **71**: A876.
15. Genest J, Cantin M. Atrial natriuretic factor. *Circulation* 1987; **75**: (Suppl. I): 118–124.
16. Grunewald C, Nisell H, Carlstrom K, Kublickas M, Randmaa I, Nylund L. Acute volume expansion in normal pregnancy and preeclampsia: Effects on plasma atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) concentrations and feto–maternal circulation. *Acta Obstetrica et Gynecologica Scandinavica* 1994; **73**: 294–299.
17. Reid DL, Goodfriend TL, Hollister MC, Phernetton TM, Rankin JHG. Effects of atrial natriuretic factor on maternal ovine vascular resistance. *Journal of Developmental Physiology* 1989; **11**: 25–28.

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Fuzzy logic control of mechanical ventilation during anaesthesia

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Summary

We have examined a new approach, using fuzzy logic, to the closed-loop feedback control of mechanical ventilation during general anaesthesia. This control system automatically adjusts ventilatory frequency (f) and tidal volume (VT) in order to achieve and maintain the end-tidal carbon dioxide fraction (FE$'_{CO_2}$) at a desired level (set-point). The controller attempts to minimize the deviation of both f and VT per kg body weight from 10 bpm and 10 ml kg^{-1}, respectively, and to maintain the plateau airway pressure within suitable limits. In 30 patients, undergoing various surgical procedures, the fuzzy control mode was compared with human ventilation control. For a set-point of FE$'_{CO_2}$ = 4.5 vol% and during measurement periods of 20 min, accuracy, stability and breathing pattern did not differ significantly between fuzzy logic and manual ventilation control. After step-changes in the set-point of FE$'_{CO_2}$ from 4.5 to 5.5 vol% and *vice versa,* overshoot and rise time did not differ significantly between the two control modes. We conclude that to achieve and maintain a desired FE$'_{CO_2}$ during routine anaesthesia, fuzzy logic feedback control of mechanical ventilation is a reliable and safe mode of control. (*Br. J. Anaesth.* 1996; **77**: 636–641)

Key words

Ventilation, mechanical. Carbon dioxide, partial pressure. Computers. Model, ventilatory mechanics. Model, computer simulation.

During anaesthetic procedures, mechanical ventilation must be controlled continuously and adjusted in order to maintain a suitable arterial carbon dioxide tension (Pa_{CO_2}). In anaesthesia for intracranial surgery, for example, hypocapnia is used deliberately to reduce brain volume and intracranial pressure. For this purpose, recommendations have been provided for the initial ventilator settings, particularly for ventilatory frequency (f) and tidal volume (VT).[1–3] These settings are corrected according to periodic measurements of arterial blood-gas tensions or by using capnometry, or both.[4] Monitoring the end-tidal carbon dioxide fraction (FE$'_{CO_2}$) allows indirect, non-invasive, breath-by-breath estimate of Pa_{CO_2} and is therefore essential for the control of the patient undergoing mechanical ventilation. As carbon dioxide production per minute ($\dot{V}_{CO_2}$) and the relation of alveolar ventilation to pulmonary perfusion ($\dot{V}$A/$\dot{Q}$) may change during anaesthesia and surgery, adjustment of the ventilator settings by the anaesthetist is required. Alternatively, automatic, closed-loop control of mechanical ventilation has been designed and applied to lung models, animals and patients, using feedback control of FE$'_{CO_2}$,[5–12] of either FE$'_{CO_2}$, inspired (FI$_{CO_2}$) or mixed expired ($F\bar{E}_{CO_2}$) carbon dioxide fraction,[13] of the end- tidal carbon dioxide partial pressure (PE$'_{CO_2}$),[14 15] Pa_{CO_2},[16–21] arterial blood pH (pH$_a$),[22] alveolar pressure over time (PA(t))[23] and gross alveolar ventilation ($\dot{V}_g$A).[24 25] The most frequently used output variables of these controllers were the ventilator settings for f, VT and respiratory minute volume (VE), but other variables such as the ratio of inspiratory to expiratory time (I/E ratio) and the inspiratory pressure support were adjusted, and carbon dioxide, delivered from a rebreathing bag and added to the inspiratory fresh gas mixture, was applied, using proportional–integral–derivative (PID) principles.[26]

Recently, there has been increasing interest in the use of so-called intelligent control techniques in biomedicine[27] and promising modern feedback control systems, based on fuzzy logic,[28] have been developed for various applications in industry, for anaesthesia and for other branches of medicine.[29–32] The software and methodology of a fuzzy controller of artificial ventilation have been developed,[23] but automatic control of FE$'_{CO_2}$ for the respiratory care of patients using fuzzy logic has not yet been performed. It was the aim of this study to compare the performance of this automatic, closed-loop control system to human control.

Patients and methods

We studied 30 patients, 10 females and 20 males, ASA I–III, mean age 47.0 (range 12–84) yr, mean weight 67.2 (41–93) kg, mean height 168.5 (153–192) cm. Written informed consent had been obtained for the study which was approved by the Ethics Committee of the medical faculty of the University of Bern. These patients were undergoing

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elective general, orthopaedic and ENT surgery. Exclusion criteria were patients of ASA classes >3, those <10 yr old (or body weight <35 kg), those whose lungs were not ventilated mechanically and where surgery was expected to last less than 2 h, and patients undergoing emergency or intracranial surgery.

Anaesthetic management, except for mechanical ventilation, was selected and performed by the attending anaesthetists according to usual practice. An additional anaesthetist, responsible for the study, was present as a supervisor. We used a modified Cicero ventilator (Drägerwerk AG, Lübeck, Germany), where f and V_T could be adjusted electronically by the control computer.

$F_{E'CO_2}$ was measured at the mouthpiece, using an airway adapter fitted with a gas sampling port and a flow and airway pressure sensor, and a side-stream infrared gas analyser (D-LITE adapter and Capnomac Ultima-SV, respectively, Datex Instrumentarium Corp., Helsinki, Finland). (Medical electrical equipment shall cause no safety hazard in normal and in single fault condition (International Standard 601-1 Clause 3.1 of the International Electrotechnical Commission.)) In the feedback control of mechanical ventilation, any failure of the Datex Capnomac Ultima-SV would be a single fault condition. Therefore, for safety reasons, an auxiliary side-stream anaesthetic gas analyser (M1025B, Hewlett Packard Co, Andover, USA), which was not implemented in the feedback control system, was used. Before the experiment, the gas monitors were calibrated according to the operator's manual. In addition to inspired/expired gas concentrations, peak airway pressure (*P*peak), plateau airway pressure (*P*plat), positive end-expiratory airway pressure (PEEP), inspired and expired volumes and pulse oximetry data were measured and displayed by the Datex Capnomac Ultima-SV. According to the manufacturer, accuracy and resolution of this monitor for $F_{E'CO_2}$ measurements were < 0.2 and 0.1 vol%, respectively, and for airway pressure measurements 0.15 and 0.1 kPa (1.5 and 1.0 cm H_2O), respectively. Values of $F_{E'CO_2}$ were displayed breath-by-breath with a response time of less than 360 ms and were transformed, together with the values of the additionally measured variables, to a serial data string and transferred every 10 s to the control computer. Values of the data string output were for $F_{E'CO_2}$, the mean value of the latest 10 s breath-by-breath values, and for *P*peak, *P*plat and PEEP, the momentary values of the previous breath.

AUTOMATIC FEEDBACK CONTROL

With the input of measured ($F_{E'CO_2}$, *P*plat) and set variables (f, V_T), the rule-based fuzzy controller determined new ventilator settings for f and V_T with a sample rate of 0.1 Hz, which compensated for the current deviation of $F_{E'CO_2}$ from the set-point ($eF_{E'CO_2}$) (fig. 1). Details on the fuzzy control algorithm are given in the appendix.

An IBM compatible personal computer was used for feedback control and for acquisition, display and storage of data. Computer programmes for these tasks were written in Modula-2 (Logitech SA, Romanel/Morges, Switzerland).

For human and automatic closed loop control of mechanical ventilation, alarm messages were displayed by the monitoring devices and the control computer if any of the preset limits of various variables were exceeded. The fuzzy control mode could be switched to human control at any time.

CLINICAL INVESTIGATIONS

In 30 patients automatic fuzzy logic feedback control of artificial ventilation was compared with human control, which was performed by five staff members, 15 residents and 10 anaesthesia nurses.

Measurements were started during maintenance of anaesthesia, independent of whether or not surgery had begun. Patients were allocated randomly

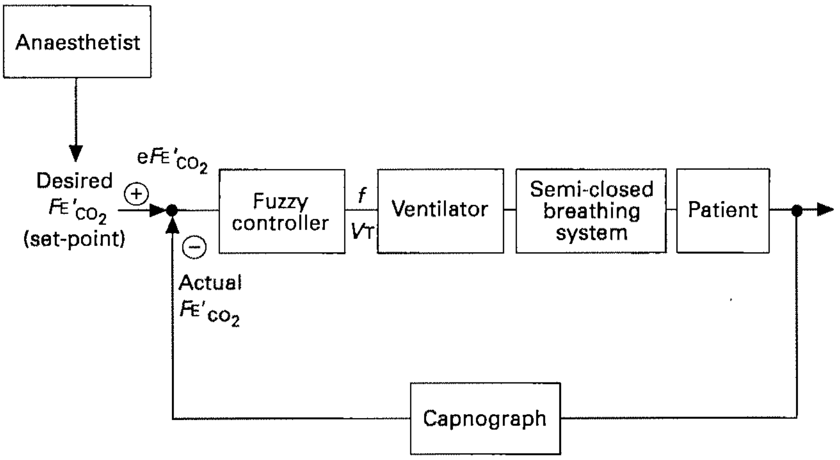

Figure 1 Block diagram of the control loop for mechanical ventilation. From the actual end-tidal carbon dioxide fraction ($F_{E'CO_2}$), measured by the capnograph (Datex Capnomac Ultima-SV), the deviation from the desired end-tidal carbon dioxide fraction ($eF_{E'CO_2}$) = desired $F_{E'CO_2}$ (set-point) − actual $F_{E'CO_2}$ was determined and compensated by changes in ventilatory frequency (f) or tidal volume (V_T), or both, computed by the fuzzy controller. Every 10 s, f and V_T were set on the ventilator (Dräger modified Cicero) by the control computer.

Table 1 Sequence of control periods for mechanical ventilation. Set-point of $F\text{E}'_{\text{CO}_2}$ = desired end-tidal carbon dioxide fraction; f = fuzzy logic control; m = manual control. Thirty investigated patients were allocated randomly to group A or B

	Period No.							
	1	2	3	4	5	6	7	8
Duration (min)	5	20	20	20	5	20	20	20
Set-point of $F\text{E}'_{\text{CO}_2}$ (vol%)	4.5	4.5	5.5	4.5	4.5	4.5	5.5	4.5
Group A	m	f	f	f	m	m	m	m
Group B	m	m	m	m	m	f	f	f

to the sequence of control periods (table 1). For each control mode and control period f and $V\text{T}$ were set by the anaesthetist (manual control) or the computer (fuzzy logic control) in order to maintain the desired $F\text{E}'_{\text{CO}_2}$. Step-changes in the desired $F\text{E}'_{\text{CO}_2}$ during periods 3, 4, 7 and 8 (table 1) had to be achieved rapidly and smoothly without considerable overshooting and consecutive oscillation of $F\text{E}'_{\text{CO}_2}$. I/E ratio, the ratio of end-inspiratory pause time to total inspiratory time (Ipause/Iratio), PEEP and the pressure limitation of the ventilator (*P*max) were set manually to 1:2, 10%, 5 and 40 mbar, respectively.

Arterial blood was sampled for blood-gas analysis at the end of periods 2 and 6 (set-point of $F\text{E}'_{\text{CO}_2}$ = 4.5 vol%) for all patients and, as a test, at the end of periods 3 or 7 (set-point of $F\text{E}'_{\text{CO}_2}$ = 5.5 vol%) for only five randomly selected patients during fuzzy ventilation control.

DATA ANALYSIS

Mean e$F\text{E}'_{\text{CO}_2}$, as a measure of accuracy, and the SD of e$F\text{E}'_{\text{CO}_2}$, as a measure of the stability of the control, were determined separately for each patient and each period of the trial programme (table 1) and each control mode. For computation of these two variables, data collected during the whole time interval of periods 2 and 6 were used, whereas for periods 3, 4, 7 and 8, only data of the last 10 min of these periods were considered. Step-changes in the set-point of $F\text{E}'_{\text{CO}_2}$ were judged by the 10–90 rise time ($T_{10\text{-}90}$) and the overshoot. For an increase in the set-point (periods 3 and 7), $T_{10\text{-}90}$ was defined as the time required for $F\text{E}'_{\text{CO}_2}$ to increase from 10% ($F\text{E}'_{\text{CO}_2}$ = 4.6 vol%) to 90% ($F\text{E}'_{\text{CO}_2}$ = 5.4 vol%) of the desired change. Because of small fluctuations in measured $F\text{E}'_{\text{CO}_2}$, $T_{10\text{-}90}$ was determined as the interval between the two events, for which $F\text{E}'_{\text{CO}_2}$ were $\geqslant$ 4.6 and $\geqslant$ 5.4 vol% for more than 1 min, respectively. For a decrease in the set-point of $F\text{E}'_{\text{CO}_2}$ (periods 4 and 8), $T_{10\text{-}90}$ was analogously defined. The overshoot was the peak absolute value of e$F\text{E}'_{\text{CO}_2}$ during the first 5 min after achievement of 90% of the step-change in the set-point.

In addition to the mean e$F\text{E}'_{\text{CO}_2}$, the SD of e$F\text{E}'_{\text{CO}_2}$, $T_{10\text{-}90}$ and the overshoot, mean f, tidal volume per kg body weight ($V\text{T}$/BW), minute volume per kg body weight ($V\text{E}$/BW), *P*peak and *P*plat were determined for any patient, control period and control mode. Using this reduced sample, means, SD and differences (fuzzy logic minus manual control) of the above mentioned variables were computed. In testing differences between the control modes the Wilcoxon signed rank test was performed. Statistical software used was SigmaStat (Jandel Scientific GmbH, Erkrath, Germany).

Results

Redundant measurements of $F\text{E}'_{\text{CO}_2}$ with both side-stream anaesthetic gas analysers revealed differences < 0.4 vol%.

Figure 2 shows the measured $F\text{E}'_{\text{CO}_2}$ during fuzzy and manual control of mechanical ventilation of the lungs of the patients.

With respect to the accuracy of the control, the mean of the averaged e$F\text{E}'_{\text{CO}_2}$ for any individual period (table 1) ranged from -0.01 to 0.00 vol% (SD 0.05 vol%) during fuzzy logic control (table 2). The minor increase in both, the corresponding range

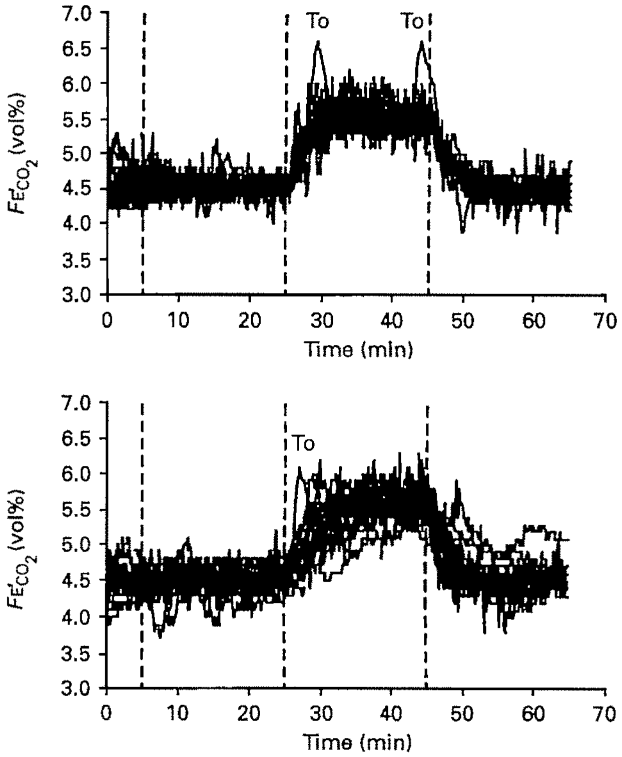

Figure 2 Measured end-tidal carbon dioxide fraction ($F\text{E}'_{\text{CO}_2}$) during fuzzy logic control (top) and manual control (bottom) of mechanical ventilation of the lungs of 30 patients according to the sequence of control periods of the trial programme (table 1). To = Transient increase in $F\text{E}'_{\text{CO}_2}$ as a result of limb tourniquet release in two patients; other peaks = inadequate feedback control. The time of initiation of data analysis and of the change in desired end-tidal carbon dioxide fraction (set-point) from 4.5 to 5.5 vol% and from 5.5 to 4.5 vol%, respectively, are indicated by the vertical broken lines.

(from -0.06 to 0.00 vol%) and SD (from 0.07 to 0.14 vol%) during manual control, yielded a statistically significant but irrelevant difference in averaged eFE'_{CO_2} values between the control modes ($P < 0.01$) when the set-point of FE'_{CO_2} was 5.5 vol%. Values for the SD of eFE'_{CO_2}, as a measure of the stability of the control, $T_{10\text{-}90}$ and the overshoot of any control period, averaged over all patients were approximately, 0.1 (SD 0.05) vol%, 350 (150) s and 0.2 (0.2) vol%, respectively (ns between control modes) (table 2). Comparison of fuzzy *vs* manual control as regards the set (*f*, *V*T/BW) and measured respiratory variables (*P*peak, *P*plat) yielded only statistically significant differences for mechanical ventilation during period 3 or 7 (set-point of FE'_{CO_2} = 5.5 vol%) for these variables (table 2). To achieve and maintain this set-point the fuzzy controller performed, on average, with slightly larger *f* and smaller *V*T/BW, and consequently smaller *P*peak and *P*plat compared with human controllers.

Blood-gas analyses revealed that the lungs of the patients were ventilated adequately with a set-point of FE'_{CO_2} = 4.5 vol% for both control modes (table 3). When the set-point of FE'_{CO_2} was 5.5 vol% the five randomly selected patients exhibited, as expected, a moderate respiratory acidosis during fuzzy control of mechanical ventilation.

Discussion

We have demonstrated that during general anaesthesia, fuzzy logic control of mechanical ventilation of the lungs of 30 patients of different ages, with various disease states and surgical procedures, was safe and reliable. Compared with human controllers, the fuzzy controller maintained desired FE'_{CO_2} with similar precision and stability and performed with a resembling dynamic response on set-point changes in FE'_{CO_2}. The breathing pattern, selected by the fuzzy controller, was within clinically acceptable ranges (fig. 2, table 2).

The ventilator settings of the fuzzy controller were based on the recommendations of Kacmarek and Venegas.[3] Except for maintaining *P*plat within suitable limits, the controller did not adapt these settings to the actual state of lung function or lung mechanics of an individual patient, which was the special feature of the lung ventilator controller described by Laubscher and co-workers[24] and Weiler, Heinrichs and Kessler.[25] It was not within the scope of this study to investigate and qualify various physiological effects as a result of automated ventilation control on respiratory and haemodynamic function. Although the results of blood-gas analyses (table 3) were clinically satisfying for both fuzzy and manual control of ventilation with a set-point of FE'_{CO_2} = 4.5 vol%, this does not prove that breathing patterns were optimal. Tweed and colleagues,[33] examining the old controversy of the influence of *V*T on the well-known impaired pulmonary gas exchange during general anaesthesia, concluded that results from previous investigations had not been consistent. Their own study revealed that patient and surgical factors were more important determinants of pulmonary gas exchange during anaesthesia than *V*T or inspired gas composition.

Table 2 Comparison of the quality, and of set and measured ventilatory variables of fuzzy logic *vs* manual control of mechanical ventilation. Values are mean (SD) or mean [SEM] for the 30 investigated patients. For period numbers see table 1. Set-point of FE'_{CO_2} = desired end-tidal carbon dioxide fraction; eFE'_{CO_2} = desired FE'_{CO_2} − actual FE'_{CO_2}; $T_{10\text{-}90}$ = 10 to 90 rise time for step changes in the set-point of FE'_{CO_2}; *f* = ventilatory frequency; *V*T/BW = tidal volume per kg body weight; *V*E/BW = minute volume per kg body weight; *P*peak = peak airway pressure; *P*plat = plateau airway pressure. Sample size = 30; †sample size = 29, size of paired differences = 28. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ (Wilcoxon signed rank test)

	4.5 (period 2 or 6)			5.5 (period 3 or 7)			4.5 (period 4 or 8)		
Set-point of FE'_{CO_2} (vol%)	Fuzzy control	Manual control	Fuzzy − manual	Fuzzy control	Manual control	Fuzzy − manual	Fuzzy control	Manual control	Fuzzy − manual
Mean eFE'_{CO_2} (vol%)	−0.01 (0.05)	0.00 (0.07)	−0.01 [0.02]	0.00 (0.05)	−0.06 (0.10)	0.06 [0.02] **	0.00 (0.05)	−0.02 (0.14)	0.02 [0.02]
SD of eFE'_{CO_2} (vol%)	0.09 (0.04)	0.11 (0.04)	−0.02 [0.01]	0.11 (0.05)	0.14 (0.06)	−0.03 [0.02]	0.08 (0.04)	0.10 (0.05)	−0.02 [0.01]
$T_{10\text{-}90}$ (s)				313 (90)	392 (179)	−79 [35]	355 (127) †	300 (189) †	45 [39] †
Overshoot (vol%)				0.26 (0.22)	0.33 (0.19)	−0.08 [0.05]	0.15 (0.16)	0.20 (0.17)	−0.05 [0.04]
Mean *f* (bpm)	9.9 (1.2)	9.6 (1.4)	0.3 [0.2]	8.5 (0.9)	7.6 (1.3)	0.9 [0.3]***	10.2 (1.1)	10.1 (1.4)	0.1 [0.2]
Mean *V*T/BW (ml kg^{-1})	9.84 (1.00)	9.91 (1.42)	−0.08 [0.16]	8.14 (1.00)	8.82 (1.58)	−0.67 [0.17]***	10.54 (1.10)	10.37 (1.54)	0.18 [0.21]
Mean *V*E/BW (ml min^{-1} kg^{-1})	98.4 (19.1)	95.7 (20.2)	2.7 [1.9]	69.9 (15.1)	67.0 (13.7)	3.0 [1.6]*	108.3 (21.1)	104.5 (21.1)	3.8 [1.9]*
Mean *P*peak (kPa)	2.05 (0.31)	2.02 (0.27)	0.03 [0.03]	1.72 (0.22)	1.80 (0.20)	−0.08 [0.02]**	2.14 (0.33)	2.16 (0.31)	−0.02 [0.04]
Mean *P*plat (kPa)	1.79 (0.24)	1.78 (0.24)	0.01 [0.03]	1.56 (0.19)	1.63 (0.18)	−0.07 [0.02]***	1.87 (0.26)	1.89 (0.27)	−0.03 [0.03]

Table 3 Arterial blood-gas analyses sampled at the end of control periods 2 and 6 of table 1 (desired end-tidal carbon dioxide fraction = 4.5 vol%) of the patients investigated during fuzzy logic and manual control of mechanical ventilation and at the end of control periods 3 or 7 (desired end-tidal carbon dioxide fraction = 5.5 vol%) of five randomly selected patients during fuzzy logic ventilation control (mean (SD) [range]). Set-point of $F\text{E}'_{CO_2}$ = Desired end-tidal carbon dioxide fraction; pH_a = arterial blood pH; Pa_{CO_2} = arterial carbon dioxide tension; Pa_{O_2} = arterial oxygen tension; Sa_{O_2} = arterial oxygen saturation; $F\text{I}_{O_2}$ = inspired oxygen fraction

Set-point of $F\text{E}'_{CO_2}$ (vol%)	4.5	4.5	5.5
Control mode	Fuzzy	Manual	Fuzzy
Sample size	27	29	5
pH_a	7.42 (0.04) [7.35–7.54]	7.42 (0.04) [7.32–7.50]	7.30 (0.06) [7.25–7.41]
Pa_{CO_2} (kPa)	5.03 (0.50) [3.97–5.87]	5.09 (0.45) [4.29–5.93]	6.70 (0.41) [6.03–7.01]
Pa_{O_2} (kPa)	19.9 (3.7) [12.1–25.2]	20.3 (3.8) [11.7–27.5]	18.9 (2.1) [15.5–20.9]
Sa_{O_2} (%)	97.3 (1.3) [92.8–98.8]	97.2 (1.1) [94.7–98.6]	96.6 (1.0) [95.0–97.6]
$F\text{I}_{O_2}$ (vol%)	34.6 (6.1) [29–56]	34.4 (6.2) [29–56]	32.4 (2.1) [29–34]

One of the aims of artificial ventilation control is to maintain Pa_{CO_2} within a small range of a desired value. In this study, however, the automatically and manually controlled variable was $F\text{E}'_{CO_2}$ as an expression of $P\text{E}'_{CO_2}$. The arterial to end-tidal $P\text{CO}_2$ difference ($Pa_{CO_2} - P\text{E}'_{CO_2}$) is small in healthy individuals, but in anaesthetized patients with altered alveolar ventilation ($\dot{V}\text{A}$) and pulmonary perfusion ($\dot{Q}$) ($\dot{V}\text{A}/\dot{Q}$ mismatch) the difference may be considerable.[34] An increased and variable end-tidal to arterial gradient may result from pre-existing cardiovascular and respiratory disease states and from the patient's physiological reactions to anaesthesia and surgery, such as variations in arterial pressure, temperature and positioning, prolonged anaesthesia, pulmonary embolism, etc. These situations, but also failing anaesthesia equipment, monitoring devices and control computer, may lead to "erroneous" control. This may be circumvented by changing the set-point of $F\text{E}'_{CO_2}$, for example after control of blood-gas tensions. Safeguards were independent alarm systems implemented on the ventilator, monitoring devices and control computer, in addition to continuous supervision of the feedback control system by the anaesthetist responsible for the study, who had some understanding of the "intelligent" systems built into the research anaesthesia workplace.

Because artificial ventilation of the lungs of a patient represents an ill-defined biological process, fuzzy logic control by its imitation of the anaesthetist's management is promising. In contrast with many studies on computer-controlled ventilation, fuzzy logic ventilation control is feasible in the "uncontrolled" clinical environment and is convenient as it relieves the anaesthetist from routine control work. It is planned to implement the control of mechanical ventilation into the developing control systems for the delivery of inhaled anaesthetics, as reported in this journal by Zbinden and co-workers[31] and Curatolo and colleagues.[32]

Appendix

FUZZY CONTROL ALGORITHM USED FOR AUTOMATIC CONTROL OF MECHANICAL VENTILATION

Basic knowledge on fuzzy logic control, which is necessary for understanding the following, has been given previously.[29–32]

Input variables of the fuzzy controller were: $\text{e}F\text{E}'_{CO_2}$ ($\text{e}F\text{E}'_{CO_2}$ = desired $F\text{E}'_{CO_2}$ − actual $F\text{E}'_{CO_2}$) (vol%) and $\text{de}F\text{E}'_{CO_2}$, which was defined as the difference between actual $\text{e}F\text{E}'_{CO_2}$ and $\text{e}F\text{E}'_{CO_2}$, 60 s before ($\text{de}F\text{E}'_{CO_2}(t_0) = \text{e}F\text{E}'_{CO_2}(t_0) - \text{e}F\text{E}'_{CO_2}(t_0 - 60\ \text{s})$) (vol%), f (bpm), tidal volume per kg body weight ($V\text{T}$/BW) (ml kg^{-1}) and Pplat (kPa). The change in minute volume per kg body weight ($\text{d}\dot{V}\text{E}$/BW) (ml min^{-1} kg^{-1}) and the change in f ($\text{d}f$) (bpm) were the output variables.

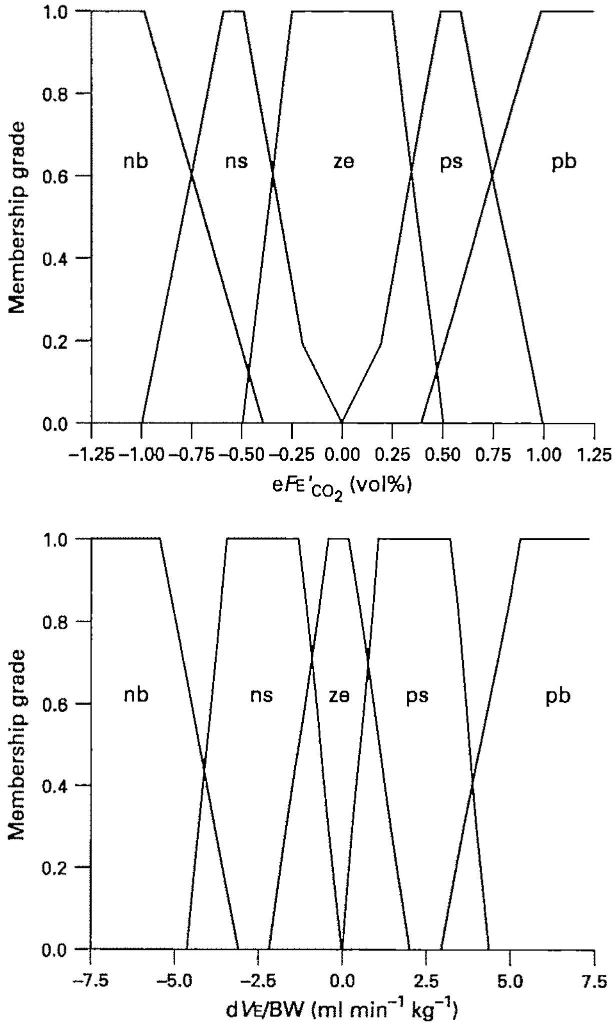

Figure 3 Subdivision of the deviation of actual from desired end-tidal carbon dioxide fraction $\text{e}F\text{E}'_{CO_2}$ = desired $F\text{E}'_{CO_2}$ − actual $F\text{E}'_{CO_2}$ and of the change in minute volume per kg body weight ($\text{d}\dot{V}\text{E}$/BW) into fuzzy sets nb (negative big), ns (negative small), ze (zero), ps (positive small) and pb (positive big), with graphs of their membership functions. For example, $\text{e}F\text{E}'_{CO_2}$ = −0.75 vol% belongs simultaneously to both the fuzzy set nb and ns, with an equal membership grade of 0.6.

Twenty-nine linguistic rules were designed, which expressed the intention to achieve and maintain the desired $F\mathrm{E}'_{\mathrm{CO_2}}$ by selection of appropriate ventilator settings and at the same time to minimize the deviation in both *f* and *V*T/BW, from 10 bpm and 10 ml kg^{-1}, respectively, and to maintain *P*plat within suitable limits (<3–4 kPa). By mean of the following examples of rules, the concept of fuzzy logic control of artificial ventilation is explained. In figure 3, typical membership functions of fuzzy sets of the input variable $\mathrm{e}F\mathrm{E}'_{\mathrm{CO_2}}$ and of the output variable d*V*E/BW are presented.

IF $\mathrm{e}F\mathrm{E}'_{\mathrm{CO_2}}$ = ns AND $\mathrm{de}F\mathrm{E}'_{\mathrm{CO_2}}$ = pb THEN d*V*E/BW = ns

If actual $F\mathrm{E}'_{\mathrm{CO_2}}$ is slightly larger than desired $F\mathrm{E}'_{\mathrm{CO_2}}$ (set-point), which implies $\mathrm{e}F\mathrm{E}'_{\mathrm{CO_2}}$ is negative small (ns), and $F\mathrm{E}'_{\mathrm{CO_2}}$ was much larger than the set-point of $F\mathrm{E}'_{\mathrm{CO_2}}$ 60 s before, which implies $\mathrm{de}F\mathrm{E}'_{\mathrm{CO_2}}$ is positive big (pb), then reduce *V*E/BW slightly, which implies d*V*E/BW is negative small (ns). Performance of this rule acts as a deceleration manoeuvre, which minimizes overshooting or oscillation of $F\mathrm{E}'_{\mathrm{CO_2}}$, or both, about the set-point.

IF *f* = ps AND *V*T/BW = pb THEN d*f* = pm

If actual *f* is small, which implies *f* is positive small (ps), and *V*T/BW is large, which implies *V*T/BW is positive big (pb), then increase *f* moderately, which implies d*f* is positive medium (pm). By maintaining *V*E/BW, *V*T/BW then decreases.

IF *P*plat = pb THEN d*f* = pb

If actual *P*plat is large (*P*plat = pb), then increase *f* considerably (d*f* = pb). By maintaining *V*E/BW, *V*T/BW and *P*plat then decrease.

Rules, sets and membership functions were designed according to clinical experience and modified in pilot studies with 14 anaesthetized patients undergoing mechanical ventilation from whom written informed consent had been obtained.

Maximum–minimum inference was used for determination of fuzzy values of output variables. Applying the centre of gravity method defuzzificated, crisp values for the ventilator settings resulted at a rate of 0.1 Hz.

In the computer programme for automatic feedback control of mechanical ventilation various safety restrictions were incorporated to keep the values of input and output variables within reasonable limits. One of these restrictions was that ventilator settings for *f* were limited to values between 6 and 20 bpm and for *V*T/BW to values between 4 and 20 ml kg^{-1}.

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References

1. Radford EP jr, Ferris BG jr, Kriete BC. Clinical use of a nomogram to estimate proper ventilation during artificial respiration. *New England Journal of Medicine* 1954; **251**: 877–884.
2. Kenny S. The Adelaide ventilation guide. *British Journal of Anaesthesia* 1967; **39**: 21–23.
3. Kacmarek RM, Venegas J. Mechanical ventilatory rates and tidal volumes. *Respiratory Care* 1987; **32**: 466–478.
4. O'Flaherty D. *Principles and Practice Series, Capnography*. London: BMJ Publishing Group, 1994.
5. Saxton GA jr, Myers G. A servomechanism for automatic regulation of pulmonary ventilation. *Journal of Applied Physiology* 1957; **11**: 326–328.
6. Frumin MJ, Lee ASJ. A physiologically oriented artificial respirator which produces N_2O–O_2 anesthesia in man. *Journal of Laboratory and Clinical Medicine* 1957; **49**: 617–622.
7. Kamiyama M, Tachibana N, Yamamura H. Automatic controller for artificial ventilation. *Japanese Journal of Anesthesiology* 1968; **17**: 1047–1048.
8. Hilberman M, Schill JP, Peters RM. On-line digital analysis of respiratory mechanics and the automation of respirator control. *Journal of Thoracic and Cardiovascular Surgery* 1969; **58**: 821–828.
9. Coles JR, Brown WA, Lampard DG. Computer control of respiration and anaesthesia. *Medical and Biological Engineering* 1973; **11**: 262–267.
10. Marsh WI, Smith WD. A flexible system for closed-loop ventilator development. *Journal of Medical Systems* 1982; **6**: 53–59.
11. Ohlson KB, Westenskow DR, Jordan WS. A microprocessor based feedback controller for mechanical ventilation. *Annals of Biomedical Engineering* 1982; **10**: 35–48.
12. Chapman FW, Newell JC, Roy RJ. A feedback controller for ventilatory therapy. *Annals of Biomedical Engineering* 1985; **13**: 359–372.
13. Giard MH, Perrin F, Bouchet P, Robert D, Pernier J. EOLE: un système de contrôle automatique de pO_2 et de pCO_2 en ventilation assistée. *Medical and Biological Engineering and Computing* 1983; **21**: 503–508.
14. Ritchie RG, Ernst EA, Pate BL, Pearson JD, Sheppard LC. Closed-loop control of an anesthesia delivery system: development and animal testing. *IEEE Transactions on Biomedical Engineering* 1987; **34**: 437–443.
15. Jantzen JP, Hennes HJ, Kleemann PP. CO_2-Rückkopplungssteuerung der Narkosebeatmung. Eine experimentelle Studie am Schweinemodell. *Anaesthesist* 1990; **39**: S101.
16. Mitamura Y, Mikami T, Sugawara H, Yoshimoto C. An optimally controlled respirator. *IEEE Transactions on Biomedical Engineering* 1971; **18**: 330–338.
17. Schulz V, Ulmer HV, Erdmann W, Kunke S, Schnabel KH. Ein Verfahren zur Pa_{CO_2}– geregelten automatischen Ventilation. *Pneumonologie* 1974; **150**: 319–325.
18. Jordan WS, Westenskow DR. Microprocessor control of ventilation using carbon dioxide production. *Anesthesiology* 1979; **51**: S380.
19. East TD, Westenskow DR, Pace NL, Nelson LD. A microcomputer-based differential lung ventilation system. *IEEE Transactions on Biomedical Engineering* 1982; **29**: 736–740.
20. Noshiro M. Design of a control system for maintaining a normal arterial pCO_2 by artificial respiration. *Medical and Biological Engineering and Computing* 1984; **22**: 418–425.
21. East TD, Andriano KP, Pace NL. Computer-controlled optimization of positive end-expiratory pressure. *Critical Care Medicine* 1986; **14**: 792–797.
22. Coon RL, Zuperku EJ, Kampine JP. Systemic arterial blood pH servocontrol of mechanical ventilation. *Anesthesiology* 1978; **49**: 201–204.
23. Vasil'eva OI, Ionov IP, Kantor PS, Ul'yanov SV. Dual control of the artificial ventilation process with use of a fuzzy controller in the feedback circuit. *Biomedical Engineering* 1989; **23**: 7–17.
24. Laubscher TP, Heinrichs W, Weiler N, Hartmann G, Brunner JX. An adaptive lung ventilation controller. *IEEE Transactions on Biomedical Engineering* 1994; **41**: 51–59.
25. Weiler N, Heinrichs W, Kessler W. The ALV-mode: a safe closed loop algorithm for ventilation during total intravenous anaesthesia. *International Journal of Clinical Monitoring and Computing* 1994; **11**: 85–88.
26. O'Hara DA, Bogen DK, Noordergraaf A. The use of computers for controlling the delivery of anesthesia. *Anesthesiology* 1992; **77**: 563–581.
27. Linkens DA, ed. *Intelligent Control in Biomedicine*. London: Taylor & Francis, 1994.
28. Zadeh LA. Fuzzy sets. *Information and Control* 1965; **8**: 338–353.
29. Martin JF. Fuzzy control in anesthesia. *Journal of Clinical Monitoring* 1994; **10**: 77–80.
30. Asbury AJ, Tzabar Y. Fuzzy logic: new ways of thinking for anaesthesia. *British Journal of Anaesthesia* 1995; **75**: 1–2.
31. Zbinden AM, Feigenwinter P, Petersen-Felix S, Hacisalihzade S. Arterial pressure control with isoflurane using fuzzy logic. *British Journal of Anaesthesia* 1995; **74**: 66–72.
32. Curatolo M, Derighetti M, Petersen-Felix S, Feigenwinter P, Fischer M, Zbinden AM. Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 245–250.
33. Tweed WA, Phua WT, Chong KY, Lim E, Lee TL. Tidal volume, lung hyperinflation and arterial oxygenation during general anaesthesia. *Anaesthesia and Intensive Care* 1993; **21**: 806–810.
34. Fletcher R. Smoking, age and the arterial–end-tidal PCO_2 difference during anaesthesia and controlled ventilation. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 355–356.

British Journal of Anaesthesia 1996; **77**: 642–644

An oral sodium citrate–citric acid non-particulate buffer in humans

J. J. HAUPTFLEISCH AND K. A. PAYNE

Summary

We have investigated the effect on the pH of the gastric fluid of a single dose of sodium citrate 0.3 mol litre^{-1} (antacid) and a solution containing sodium citrate dehydrate (100 mg ml^{-1}) with citric acid monohydrate (66 mg ml^{-1}) (buffer). The dose for both solutions was 0.4 ml kg^{-1} via a nasogastric tube. Each group comprised 10 patients undergoing neurosurgical operations of 5–7 h duration. A control group of 10 patients received no gastric solution. The pH of the gastric aspirate was measured hourly using a Metrohm 632 digital pH meter (Synectics Medical, Sweden). Mean baseline gastric pH was 2.64 (SD 1.71). In the control group, pH increased to 4.4 (1.51) at 5 h, returning to baseline at 7 h. In the antacid group, pH increased to 6.11 (0.47) at 15 min and decreased to 3.70 (1.94) at 7 h ($P < 0.01$). In the buffer group, pH was stable at 3.80–3.95 (0.22) over 7 h ($P > 0.01$). Total mean gastric aspirate was 0.5 ml kg^{-1}. (*Br. J. Anaesth.* 1996; **77**: 642–644)

Key words
Gastrointestinal tract, pH. Acid–base equilibrium, pH. Acid–base equilibrium, buffers. Gastrointestinal tract, antacids. Fluids, oral.

Aspiration pneumonitis from inhaling acid gastric content is an anaesthetic hazard. This is associated with a gastric pH of less than 2.5, and factors that contribute to this include prolonged fasting time, ileus, unconsciousness and the stress response to surgery.[1–3] These factors apply to patients undergoing prolonged surgical procedures, so that the extubation and recovery phases of anaesthesia have the potential for regurgitation and aspiration of gastric content.[2 4]

Antacid therapy with an alkaline solution such as sodium citrate 0.3 mol litre^{-1} is used commonly to antagonize gastric acidity in the preanaesthetic phase. However, reported problems include short duration of action (2–4 h),[5 6] increase in gastric volume[4] and rebound gastric acid secretion.[7]

A buffer solution of sodium citrate dihydrate 100 mg ml^{-1} and citric acid monohydrate 66 mg ml^{-1} is designed to buffer the gastric content, rather than neutralize it[8] (Pneucid, Narkopharm). This is postulated to have a longer duration of action than sodium citrate and to prevent rebound gastric secretion, thus improving the safety profile at extubation.

It had been shown that this buffer solution did not cause chemical pneumonitis in canine lungs,[8] hence human trials could proceed. We studied the efficacy of this agent in controlling gastric pH in humans undergoing anaesthesia of 5 h or more duration.

Patients and methods

We undertook a prospective, randomized study in 30 neurosurgical patients, aged 18 yr or more. Surgery was for excision of cerebral tumours or clamping of cerebral aneurysms and duration was 5 h or longer. Patients were free of other pathology and were conscious and orientated before operation. Preoperative medication included dexamethasone for patients with tumours, and labetalol and diazepam for aneurysm patients. The hospital Ethics Committee gave consent for the study and written informed consent was obtained from the patients.

We studied three groups of 10 patients each: the control group received no gastric medication, the antacid group received sodium citrate 0.3 mol litre^{-1} (0.4 ml kg^{-1}),[9] and the buffer group received a solution containing sodium citrate dehydrate 100 mg ml^{-1} with citric acid monohydrate 66 mg ml^{-1} at 0.4 ml kg^{-1}.[8]

Premedication comprised oral diazepam 0.15 mg kg^{-1} and induction of anaesthesia was with thiopentone 3–5 mg kg^{-1} i.v. Neuromuscular block was produced with an infusion of atracurium 0.5 mg kg^{-1} h^{-1} and morphine 10–30 mg i.v. was given for analgesia. The patient's lungs were ventilated with 1–2% isoflurane and 50% nitrous oxide in oxygen as needed. Ventilation was set to provide an end-expired carbon dioxide concentration of 3–3.5% and a 20° head-up tilt was used. Labetalol was used to maintain heart rate at less than 80 beat min^{-1} and a 0.01% sodium nitroprusside infusion provided hypotension when needed. Mean arterial pressures were maintained at 80 mm Hg except in some aneurysm cases when mean pressures of 70 mm Hg were used during clamping. Normal temperatures were maintained using convective air blankets.

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Standard monitors included oximetry, capnography, oesophageal temperature, electrocardiography, direct arterial pressure, central venous pressure, neuromuscular block and urinary catheter. Arterial blood was obtained hourly for measurement of blood-gas tensions, electrolyte concentrations and acid–base balance.

When patients' lungs had been intubated and stabilized, a 10-gauge orogastric tube was passed and its position verified by aspirating 2 ml of gastric content. The test solutions, 0.4 ml kg^{-1}, were then injected down the gastric tube and flushed with 5 ml of sterile water. The control group received no fluid down their gastric tube. Fifteen minutes thereafter, 2 ml of gastric content were aspirated. This was repeated every 60 min for the duration of the anaesthetic. The gastric tube was removed before tracheal extubation, after aspirating as much volume as possible. Patients were supine at this time.

The pH of the samples was measured in a Metrohm 632 Digital pH meter (Synectics Medical, Sweden). This was calibrated before each patient at a temperature of 36 °C using the manufacturer's buffer solution.

Data were compared by analysis of variance and multiple linear regression analysis. This compared the pH values and their changes over time in the three groups. $P = 0.01$ was taken as significant.

Results

The three groups were comparable in age, weight, sex and duration of surgery (table 1). pH values are shown in figure 1. There were no differences at baseline. Overall mean pH was 2.64 (SD 1.71), with 19 patients having values of less than 2.5. However, at 15 min, both groups had pH values significantly higher than that of the control group (2.18 (1.00); $P < 0.01$). The antacid group had a significantly higher pH (6.11 (0.47)) than the buffer group (3.92 (0.24)) ($P < 0.01$).

Over the next 7 h the pH of patients in the antacid group decreased steadily from the peak at 15 min to 3.70 (1.94) at 7 h. Patients in the buffer group remained stable, with mean pH values of 3.80–3.95 (0.22) throughout this time. Mean pH values in the control group increased to a plateau of 4.10–4.41 (1.51) at 2–5 h, thereafter returning to baseline values at 7 h. Mean pH values in the antacid group were significantly different from those of the control and buffer groups for 4 h ($P < 0.01$) but there was no difference between mean values in the control and buffer groups , except at 15 min.

While mean pH values were greater than 2.5, individual patient values revealed potentially dangerous decreases. In the control group, two patients had pH values of less than 2.5 throughout the study and four others had pH values less than 2.5 for the first hour, one of whom returned to less than 2.5 by 7 h. In the antacid group, one patient had a pH of 2.08 at 5 h which decreased to 1.46 at 7 h. No patient in the buffer group had a pH value less than 3.71 during the study and the highest value was 4.43.

In the two groups who received oral solutions, total gastric volume aspirated during the study was approximately 0.5 ml kg^{-1}. Mean volumes were 42 (12.1) ml in the antacid group and 39.2 (23.3) ml in the buffer group. The control group had a significantly lower mean volume (20.3 (6.4) ml; $P < 0.01$). Final residual volumes aspirated were 27.6 (12.4) ml, 26.7 (23.0) ml and 8.8 (5.6) ml, respectively ($P < 0.01$).

Discussion

Our study has confirmed that preoperative fasting adults are likely to have gastric pH values that put them at risk of the aspiration pneumonitis syndrome[1,4]; 63% had baseline pH values of less than 2.5. The response to both of the test solutions was rapid, safe levels being obtained by 15 min. As the buffer solution has a pH of 4.8,[8] the initial increase in gastric pH was less than that with sodium citrate 0.3 mol $litre^{-1}$, but the pH values remained within a stable mean range of 3.80–3.94 for 7 h. These values would avoid the danger of rebound acid secretion which might result from gastric values of greater than 6.[7]

In contrast, sodium citrate 0.3 mol $litre^{-1}$ has a pH of 8.4[8] and it caused mean pH to increase to greater than 6 for 1 h. In one patient this was followed by a sustained decrease to less than 2.5, possibly because of rebound acid secretion.[7] This rebound phenomenon is one of the reasons why sodium citrate 0.3 mol $litre^{-1}$ is recommended as a regular 2–4 hourly regimen for women in labour.[5,6] The more prolonged effect seen here would be a

Table 1 Patient data and operations performed (mean (SD or range) or number)

	Group		
	Control	Antacid	Buffer
Age (yr)	37.3 (20–80)	34.5 (20–65)	37.3 (18–74)
Weight (kg)	79 (5.43)	83 (6.12)	78 (4.97)
Sex (M/F)	6:4	5:5	4:6
Surgery tumours	6	6	7
Duration of surgery (h)	5 (1.44)	5 (1.63)	5 (0.95)

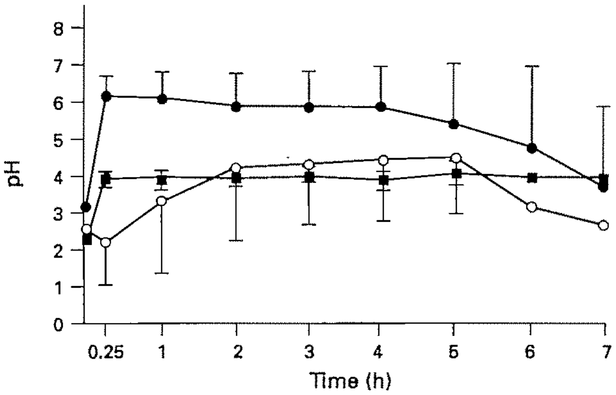

Figure 1 Mean (SD) pH values. At 15 min, pH values in the buffer (■) and antacid (●) groups were significantly higher than those in the control group (○) ($P < 0.01$). The pH values in the antacid group were significantly higher than those in the two other groups for 4 h. The buffer and control groups had two and one patient, respectively, after 6 h, hence no SD are given after 5 h.

result of the influence of the anaesthetic on the gastric mucosa during non-stressful surgery,[4] compared with a woman in active labour. Halothane anaesthesia is known to decrease gastric acid production via a directly depressant effect on acid producing cells.[10] It is likely that isoflurane would have a similar effect. This would explain the increase in mean gastric pH in the control group to 3–4 for the duration of the anaesthetic. However, this was very variable and six of 10 patients had pH values of less than 2.5 at some stage during the anaesthetic.

The danger of developing the pulmonary acid aspiration syndrome is also related to the volume inhaled. Primate data indicate that a volume in excess of 0.8 ml kg^{-1}, together with a low pH, is needed.[11] Therefore, any oral solution should not result in volumes greater than this. Both of the test solutions gave total aspirated gastric volumes of 0.5 ml kg^{-1}. While these are increased compared with resting gastric volumes of 0.3–0.4 ml kg^{-1} reported from fasting adults,[12 13] they are below the suggested danger level of 0.8 ml kg^{-1}.

From the duration of action of the buffer solution, systemic absorption was not rapid. Nevertheless, the potential effects on the systemic system need to be considered. No effects were seen and hourly arterial acid–base and electrolyte values were unaffected. This is to be expected, as the agents in the buffer solution were used for many years as anticoagulants (acid citrate glucose anticoagulant) in transfused blood.[14 15] The mean volume administered (32 ml) contained a similar amount of sodium citrate dihydrate and citric acid monohydrate as was present in 2 u. of blood.

Patients undergoing neurosurgery and other prolonged procedures are likely to be in the high dependency unit for some time. Because of the increased incidence of stress ulcers developing at gastric pH values of less than 3[16 17] and the decrease in gastric bacterial barrier at pH values greater than 4.5,[17 18] a desired pH range of 3–4.5 has been proposed.[19] Therapy to achieve this should commence as early as possible. In this regard, sodium citrate 0.3 mol $litre^{-1}$ was inadequate, with mean pH values of 5–6 for 5 h with one less than 2.5. The buffer solution produced closely grouped values within the proposed range for the 7 h studied. If used in a high dependency unit, duration of effective gastric pH control would need to be monitored from nasogastric tube aspirate.

We conclude that the buffer solution of sodium dihydrate (citric acid monohydrate) was an effective gastric acid inhibitor, with a duration of action of 7 h in neurosurgical operations.

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References

1. Gibbs CP, Modell JH. Pulmonary aspiration of gastric contents, pathophysiology, prevention and management. In: Miller RD, ed. *Anaesthesia,* 4th Edn. New York: Churchill Livingstone, 1994; 1437–1464.
2. Morgan M. Control of intragastric pH and volume. *British Journal of Anaesthesia* 1984; **56**: 47-57.
3. Hester JB, Heath ML. Pulmonary acid aspiration syndrome. Should prophylaxis be routine. *British Journal of Anaesthesia* 1977; **49**: 595–599.
4. Kallar SK, Everett LL. Potential risks and preventive measures for pulmonary aspiration. New concepts in preoperative fasting quidelines. *Anesthesia and Analgesia* 1993; **77**: 171–182.
5. Brocke-Utne JG, Moshal MG, Downing JW, Spitaels JM, Stiebel R. Fasting volume and acidity of stomach contents associated with gastrointestinal symptoms. *Anaesthesia* 1977; **32**: 749–752.
6. Roberts RB, Shirley MA. The obstetrician's role in reducing the risk of aspiration pneumonitis with particular reference to the use of oral antacids. *American Journal of Obstetrics and Gynecology* 1976; **124**: 611–617.
7. Lahiri SK, Thomas TA, Hodgson RM. Single dose antacid therapy for the prevention of Mendelson's syndrome. *British Journal of Anaesthesia* 1973; **45**: 1143–1146.
8. Payne KA, Wandrag S, Griessel P. An oral sodium citrate–citric acid non-particulate buffer. In vitro buffering ability and potential for pulmonary toxicity. *Drug Investigations* 1993; **6**: 218–222.
9. Morgan N. Getting there. *Anaesthesia* 1991; **46**: 709–711.
10. Christensen V, Skousted P. Effects of general anaesthetics on the pH of gastric contents in man during surgery. *Acta Anaesthesiologica Scandinavica* 1975; **19**: 49–54.
11. Raidoo DM, Rocke DA, Brocke-Utne JG, Marszalek A, Engelbrecht HE. Critical volume for pulmonary acid aspiration. Reappraisal in a primate model. *British Journal of Anaesthesia* 1990; **65**: 248–250.
12. Agarwal A, Chari P, Singh H. Fluid deprivation before operation. *Anaesthesia* 1989; **44**: 632–634.
13. McGrady EM, MacDonald AG. Effect of the pre-operative administration of water on gastric volume and pH. *British Journal of Anaesthesia* 1988; **60**: 803–805.
14. Donaldson MDJ, Seaman MJ, Park GR. Massive blood transfusion. *British Journal of Anaesthesia* 1992; **69**: 621–630.
15. Isbister JP. Haemotherapy for acute haemorrhage. *Anaesthesia and Intensive Care* 1984; **12**: 217–228.
16. Krier C, Böhrer H, Jürs G. Continuous intragastric pH measurement in intensive care patients treated with ranitidine and tube feeding. *Anasthesie Intensivtherapie Notfallmedizin* 1990; **25**: 10–3.
17. Eddleston JM, Vohra A, Scott P. A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate or ranitidine treated intensive care patients. *Critical Care Medicine* 1991; **19**: 1491–1496.
18. Apte NM, Karnod DR, Medhekar TP. Gastric colonization and pneumonia in critically ill patients receiving stress ulcer prophylaxis. *Critical Care Medicine* 1992; **20**: 590–593.
19. Atanassoff PG, Sorin JB, Weiss BM, Landefeld K, Alon E, Rohling R. The time course of gastric pH changes induced by omeprazole and ranitidine. A 24 hour dose response study. *Anesthesia and Analgesia* 1995; **80**: 975–979.

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LABORATORY INVESTIGATIONS

Effects of local anaesthetics on carrageenan-evoked inflammatory nociceptive processing in the rat

J. BURITOVA, D. FLETCHER, P. HONORÉ AND J.-M. BESSON

Summary

We have assessed the effects of intraplantar local anaesthetics (bupivacaine and lignocaine) on carrageenan-induced oedema, mechanical allodynia and spinal *c-fos* protein expression. Mechanical allodynia was evaluated using the vocalization threshold to paw pressure (VTPP) every 30 min until 60, 180 or 240 min after administration of carrageenan. Peripheral oedema, mechanical allodynia and spinal *c-fos* protein expression were maximal 180 min after carrageenan. Lignocaine did not influence either oedema or VTPP, but reduced spinal *c-fos* expression at 60 min after carrageenan without later effects. Bupivacaine induced an increase in VTPP at 30 and 60 min, limitation of oedema at 60 min and a reduction in spinal *c-fos* expression at 60 and 180 min, but these effects were not present 240 min after carrageenan. Intraplantar infiltration with lignocaine and bupivacaine before carrageenan transiently limited signs of inflammatory pain but did not prevent them. (*Br. J. Anaesth.* 1996; **77**: 645–652)

Key words
Analgesia, pre-emptive. Pain, experimental. Genetic factors, proto-oncogenes. Anaesthetics local. Spinal cord. Rat.

Bupivacaine and lignocaine, long- and short-acting local anaesthetics respectively, are used in both acute and chronic pain therapy (see references in Bonica and Butler[1]). There is evidence that pain processing may be reduced by pre-administration of various agents (e.g. opioids, local anaesthetics, non-steroidal anti-inflammatory drugs (NSAID)) leading to the concept of pre-emptive analgesia.[2] However, this concept is still debated[3] and few clinical studies have confirmed the clinical significance of pre-emptive analgesia.[4–6] Administration of local anaesthetics before tissue injury may prevent peripheral and central sensitization of the nervous system induced by nociceptive input (see references in Coderre and colleagues[4]). The pre-emptive analgesic effect of local anaesthetics has been observed in different animal models of pain (see references in Coderre and colleagues[4]).

In this study, we have investigated the possible pre-emptive effects of local anaesthetics (lignocaine and bupivacaine) in the carrageenan model of inflammatory pain in rats.[7] As shown previously, intraplantar injection of carrageenan induces ipsilateral inflammation (see references in Kocher and colleagues[8]) associated with mechanical allodynia[9] and *c-fos*-protein-like immunoreactivity (*c-fos* LI) in the ipsilateral dorsal horn of the spinal cord.[10–12] The method based on the immunoreactivity of *c-fos*-protein is used widely as a form of neuronal-activity mapping (see references in Morgan and Curran[13]). For a recent review of the mechanisms of expression of *c-fos* protein within the nervous system see Hughes and Dragunow.[14] Many studies following the original report[15] have provided evidence that various noxious stimulations evoked expression of *c-fos* protein in spinal neurones (see references in Zimmermann and Herdegen[16]), thus providing an indirect marker of neurones involved in spinal nociceptive transmission. In our previous studies, we used immunohistochemical revelation of spinal *c-fos* expression in the carrageenan model of inflammatory pain to assess the effects of analgesic/anti-inflammatory drugs, including systemic[17] and intraplantar[18] morphine and various systemic NSAID (see Buritova and colleagues[19] and references therein). In this study, we have combined behavioural and immunohistochemical approaches to investigate the effects of pre-administered intraplantar local anaesthetics in carrageenan-induced inflammatory pain in rats.

Materials and methods

EXPERIMENTAL ANIMALS

Experiments were performed on 52 adult male albino Sprague–Dawley rats (Charles River, France; 48 carrageenan-stimulated and four non-stimulated rats), weighing 225–250 g. Rats were acclimatized to the laboratory for 8 days before the experiment. Rats were tested using the vocalization threshold to paw pressure (VTPP) and were trained in the experimental conditions during the last 2 days before the experiment. The

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ethics guidelines of the IASP were followed for investigations of experimental pain in conscious animals.[20]

DRUG ADMINISTRATION

Peripheral inflammation was induced by intraplantar injection of carrageenan (λ-carrageenan, Sigma; 6 mg per 150 μl of saline (0.9% NaCl)) in the right hind paw of the non-anaesthetized rat. In this study, control rats receiving intraplantar injection of saline were not included as we have shown previously negligible spinal *c-fos* expression after intraplantar saline (<5 *c-fos* LI neurones per section L4–L5) which was not significantly different from that observed in non-stimulated rats.[12] The preliminary unpublished study demonstrated that intraplantar administration of local anaesthetics (0.5% Marcaine, 2% xylocaine) without carrageenan injection did not induce spinal *c-fos* expression significantly different from that observed in intraplantar saline injected rat (<5 *c-fos* LI neurones per section L4–L5).

Intraplantar bupivacaine (0.5% Marcaine, Astra, France) and lignocaine (2% Xylocaine, Astra, France) were injected into the right hind paw of non-anaesthetized rats (200 μl for both drugs) 5 min before intraplantar injection of carrageenan. The timing, concentration and volume of local anaesthetic were chosen according to a previous study to obtain complete anaesthesia of the paw before injection of carrageenan.[21] Control carrageenan rats received 200 μl of saline under the same experimental conditions. Intraplantar injections of carrageenan or local anaesthetic were made subcutaneously with a 25-gauge needle.

MEASUREMENT OF CARRAGEENAN-INDUCED PERIPHERAL OEDEMA

Two indicators of peripheral oedema, ankle and paw diameters, were measured with a calliper square, immediately before perfusion at 60, 180 or 240 min after injection of carrageenan. Ankle and paw diameters of carrageenan-stimulated and non-stimulated rats were measured. Oedema was determined as percentage increases in ankle and paw diameters of carrageenan-treated rats compared with non-stimulated rats.

TEST OF VOCALIZATION THRESHOLD TO PAW PRESSURE

The vocalization threshold to paw pressure (VTPP) was measured using a Basile Analgesimeter (Apelex, tip diameter of the probe = 1 mm) according to a method adapted from the Randall-Selitto description.[22] All VTPP measurements were performed blind by the same investigator. For each rat, the thresholds for vocalization (mean of two values), expressed in grams (g), were determined by applying increasing pressure to the right hind paw until an audible squeak was elicited. A control value was determined before injection of carrageenan. We then determined, at each time after carrageenan, two stable consecutive thresholds, which were averaged. This criterion of the VTPP was chosen according to a previous study,[22] as it represents a more integrated nociceptive behaviour than paw withdrawal. The choice of a cut-off value was necessary to limit injury to the paw and excessive stimulation of the nociceptors. The cut-off value was 600 g and was considered sufficient to represent an anaesthetic state.

IMMUNOHISTOCHEMISTRY FOR EVALUATION OF SPINAL C-*FOS* PROTEIN EXPRESSION

As demonstrated previously, carrageenan-evoked spinal *c-fos* expression was detected at 60 min[17] and was maximal at 180 min[12] after intraplantar injection of carrageenan. Therefore, in this study of the time course of the local anaesthetic effects, rats were perfused at various times after injection of carrageenan: 60, 180 and 240 min, immediately after the last test of VTPP. As described previously (see references in Buritova and colleagues[19]), rats were deeply anaesthetized (pentobarbitone (Sanofi) 55 mg kg^{-1} i.p.) and perfused intracardially with phosphate-buffered saline (PBS) 0.1 mol $litre^{-1}$ followed by 4% paraformaldehyde in phosphate buffer (PB) 0.1 mol $litre^{-1}$. The spinal cord was removed, post-fixed for 4 h and cryoprotected in 30% sucrose overnight. Frozen serial frontal sections (40 μm) of the lumbar L4–L5 segments were cut. Immunohistochemistry of the free floating sections was performed with polyclonal antiserum, generated in rabbits, directed against the *c-fos* protein (Oncogene Science Inc., Ab-2 solution 0.1 mg ml^{-1} diluted 1:4000), using the conventional avidin–biotin–peroxidase complex method with visualization by 1-naphthol ammonium carbonate solution (for more details see methods in Buritova and colleagues[19]).

COUNTING OF SPINAL C-*FOS* LI NEURONES

As described previously (see Buritova and colleagues[19] and references therein), distribution of *c-fos* LI neurones was studied in four defined regions: superficial laminae (laminae I–II), nucleus proprius (laminae III–IV) and neck (laminae V–VI) of the dorsal horn and, in addition, ventral horn (laminae VII–X; ventral) of the spinal cord. For each rat, two counts were made: (1) the total number of *c-fos* LI neurones in the grey matter for 10 sections through L4–L5 segments, and (2) in these 10 sections, the number of *c-fos* LI neurones in the four defined regions. Plotting and counting the *c-fos* LI neurones were performed blind to the experimental condition. Statistical analysis was performed using analysis of variance (ANOVA) and the Fisher's protected least squares difference test (Fisher's PLSD test) for multiple comparisons. The effects of local anaesthetics on peripheral oedema, VTPP and number of spinal *c-fos* LI neurones were determined compared with controls (control group).

EXPERIMENTAL DESIGN

To evaluate the time course of the effects of local anaesthetics on carrageenan-induced inflammatory nociceptive processing, the experiment was performed in three different series. In each series, rats were perfused immediately after the last test of VTPP.

In the first series (n = 18), rats in the control, lignocaine and bupivacaine groups were tested for VTPP every 30 min for 60 min after administration of carrageenan at which time rats were perfused. In the second series (n = 18), rats in the control, lignocaine and bupivacaine groups were tested for VTPP every 30 min for 180 min after administration of carrageenan at which time rats were perfused. In the third series (n = 12), control and bupivacaine groups were tested for VTPP every 30 min for 240 min after administration of carrageenan at which time rats were perfused. In this series, the lignocaine group was not included as intraplantar pre-administration of lignocaine was not efficacious as early as 180 min after carrageenan administration.

In these experimental series, three distinct groups of rats were defined: in the control group (n = 6 for each time), rats received saline 200 μl, 5 min before administration of carrageenan and were tested for VTPP after carrageenan; in the bupivacaine group (n = 6 for each time) rats received bupivacaine 200 μl, 5 min before carrageenan and were tested for VTPP after carrageenan; in the lignocaine group (n = 6 for each time) rats received lignocaine 200 μl, 5 min before carrageenan and were tested for VTPP after carrageenan.

Results

DEVELOPMENT OF CARRAGEENAN-EVOKED OEDEMA

In the control group, 60, 180 and 240 min after intraplantar administration of carrageenan, both paw (0.8 (SEM 0.1), 1.1 (0.1) and 1.1 (0.1) cm, respectively) and ankle (0.8 (0.1), 1.2 (0.1) and 1.1 (0.1) cm, respectively) diameters were increased significantly compared with carrageenan non-stimulated rats (mean values for paw and ankle diameters: 0.5 (0.1) and 0.7 (0.1) cm, respectively). Inflammatory oedema was not present in the contralateral hind paw at each time.

At 60 min after carrageenan, in the bupivacaine group, carrageenan-evoked ankle oedema (0.75 (0.02) cm) was reduced slightly compared with the control group ($P < 0.01$) but paw oedema was not influenced. Bupivacaine had no effect on paw or ankle oedema at 180 and 240 min after carrageenan.

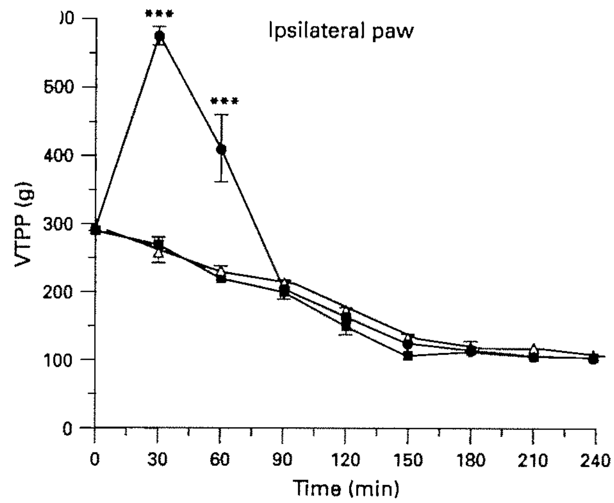

Figure 1 Effects of intraplantar 0.5% bupivacaine (●) and 2% lignocaine (■) on VTPP over 4 h after administration of carrageenan. From 0 to 60 min: n = 18; from 60 to 180 min: n = 12; from 180 to 240 min: n = 6. Results are expressed as absolute mean (SEM) of the threshold value, each 30 min after intraplantar carrageenan. Significance compared with control group (Δ) was performed using ANOVA and Fisher's PLSD test (***$P < 0.001$). The study of the effect of lignocaine at 4 h was not performed.

In the lignocaine group, paw and ankle oedema were not influenced at each time after carrageenan.

CARRAGEENAN-EVOKED DECREASE OF VTPP

The results were similar for the three series and were therefore pooled (see fig. 1).

Intraplantar carrageenan decreased VTPP at each time, with a final decrease to 35% of control values at 240 min after carrageenan (fig. 1). Overall, VTPP decreased from 288 (7) g at time 0 min, to 100 (3) g at 240 min after carrageenan (fig. 1).

In the lignocaine group, VTPP never reached the cut-off value at each time after carrageenan. At 60 and 180 min after carrageenan, VTPP decreased to 76% and 37% of control values, respectively, reflecting the development of mechanical allodynia. Overall, VTPP decreased from 287 (6) g at time 0 min to 108 (9) g at 180 min after carrageenan (fig. 1).

In the bupivacaine group, VTPP reached the cut-off value in 95% of rats at 60 min after carrageenan. At later times, 180 and 240 min, VTPP decreased to 37% and 35% of control values, respectively. Overall, VTPP decreased from 287 (6) g at time

Table 1 Effects of intraplantar 0.5% bupivacaine and 2% lignocaine on the number of c-*fos* LI neurones in the superficial (I–II) and deep (V–VI) laminae of the dorsal horn and in the ventral horn (Ventral) of the L4–L5 segments of the rat spinal cord at 1, 3 and 4 h after intraplantar carrageenan. Results are expressed as the absolute mean (SEM) of the number of c-*fos* LI neurones per section for each region. Significance of the effects of both anaesthetics, compared with the control group, was performed using ANOVA and Fisher's PLSD test (**$P<0.01$, ***$P<0.001$). The effect of lignocaine at 4 h was not performed

	No. c-*fos*/LI neurones/section of L4–L5 segments											
	1 h after carrageenan				3 h after carrageenan				4 h after carrageenan			
Group	Total	I–II	V–VI	Ventral	Total	I–II	V–VI	Ventral	Total	I–II	V–VI	Ventral
Control	101 (8)	45 (3)	38 (5)	12 (1)	200 (15)	59 (4)	87 (6)	43 (5)	141(6)	51 (2)	54 (4)	27 (1)
Bupivacaine	40 (3)***	16 (3)***	16 (1)***	5 (1)***	143 (8)**	49 (2)	60 (5)***	28 (3)**	130 (12)	45 (4)	51 (4)	27 (3)
Lignocaine	64 (6)***	25 (3)***	23 (2)***	9 (2)	187 (12)	64 (6)	79 (4)	34 (3)	—	—	—	—

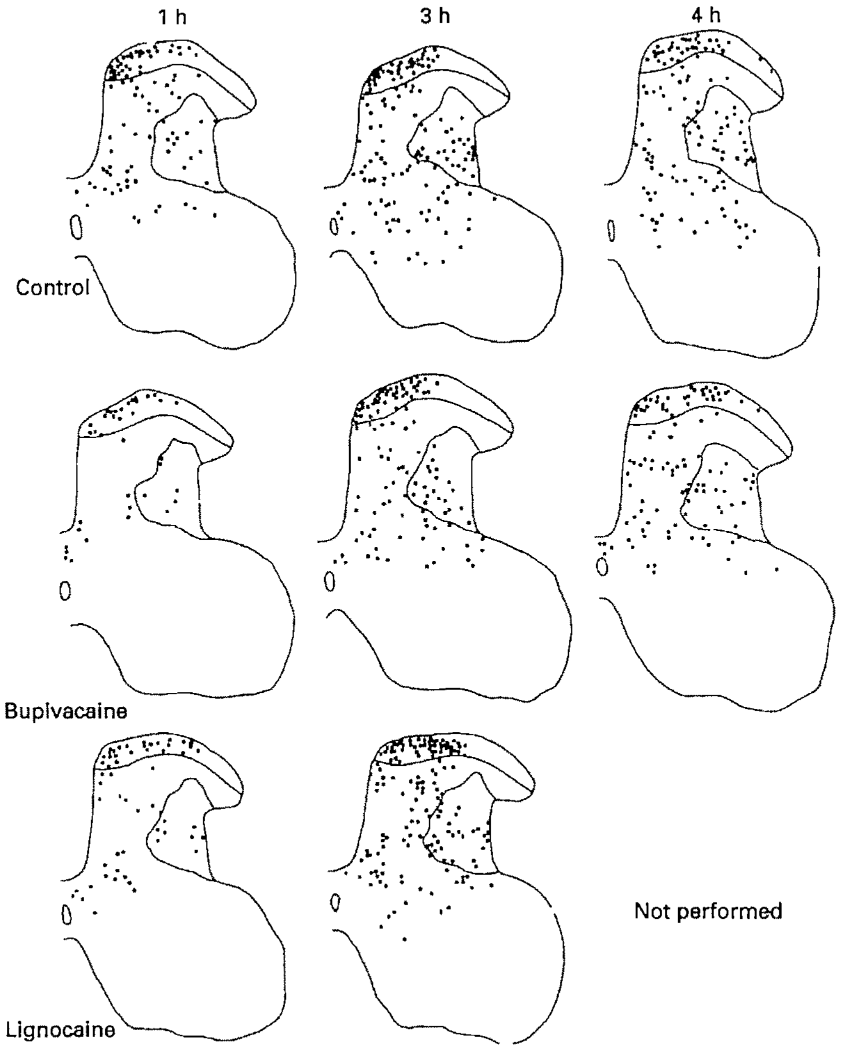

Figure 2 Camera lucida drawings of individual sections (40 μm) of the L4–L5 segments of the rat spinal cord showing effects of intraplantar 0.5% bupivacaine and 2% lignocaine on the number of spinal c-*fos* LI neurones, at 1, 3 and 4 h after intraplantar administration of carrageenan. The boundaries of the superficial laminae and the reticular part of the neck of the dorsal horn are outlined; each dot represents one c-*fos* labelled nucleus (one c-*fos* LI neurone).

0 min to 100 (3) g at 240 min after carrageenan (fig. 1). The mean duration of analgesic effect of bupivacaine was 55 (16) min.

TIME COURSE OF CARRAGEENAN-EVOKED SPINAL C-*FOS* EXPRESSION

In the control group, the total number of c-*fos* LI neurones was greatly increased in the ipsilateral spinal cord at 60, 180 and 240 min after carrageenan (fig. 2, fig. 4A; table 1). At all times after carrageenan, spinal c-*fos* LI neurones of the control group were located predominantly in laminae I–II and V–VI of the dorsal horn of the lumbar spinal cord (fig. 2, fig. 4B,C, table 1). At 60, 180 and 240 min after carrageenan, the number of c-*fos* LI neurones in the nucleus proprius (laminae III–IV: 6 (1), 10 (2) and 8 (1) c-*fos* LI neurones per L4–L5 section, respectively) was moderate compared with the total number of c-*fos* LI neurones per L4–L5 section (101 (8), 200 (15) and 141 (6), respectively) (table 1). At each time, c-*fos* LI neurones were almost absent in the contralateral spinal cord (<5 c-*fos* LI neurones per L4–L5 section).

At 60 min after intraplantar carrageenan, carrageenan-evoked spinal c-*fos* expression in the bupivacaine and lignocaine groups was significantly different from that observed in the control group, for both the total number of c-*fos* LI neurones in segments L4–L5 (F (3, 20) = 16.17; $P < 0.001$) and their laminar distribution (F (3, 80) = 34.20; $P < 0.001$). Intraplantar pre-administration of both bupivacaine and lignocaine reduced the total number of c-*fos* LI neurones induced at 60 min after carrageenan (60 (3) % and 37 (6) % reduction of control group values, respectively; $P < 0.001$ for both drugs) (fig. 4A, table 1). Furthermore, in both the bupivacaine and lignocaine groups, the significant reduction in the number of superficial (laminae I–II: 63 (6) % and 44 (6) % reduction of control group values, respectively; $P < 0.001$ for both drugs) (fig. 3) and deep (laminae V–VI: 59 (3) % and 39 (5) % reduction of control group values, respectively; $P < 0.001$ for both drugs) c-*fos* LI neurones was observed

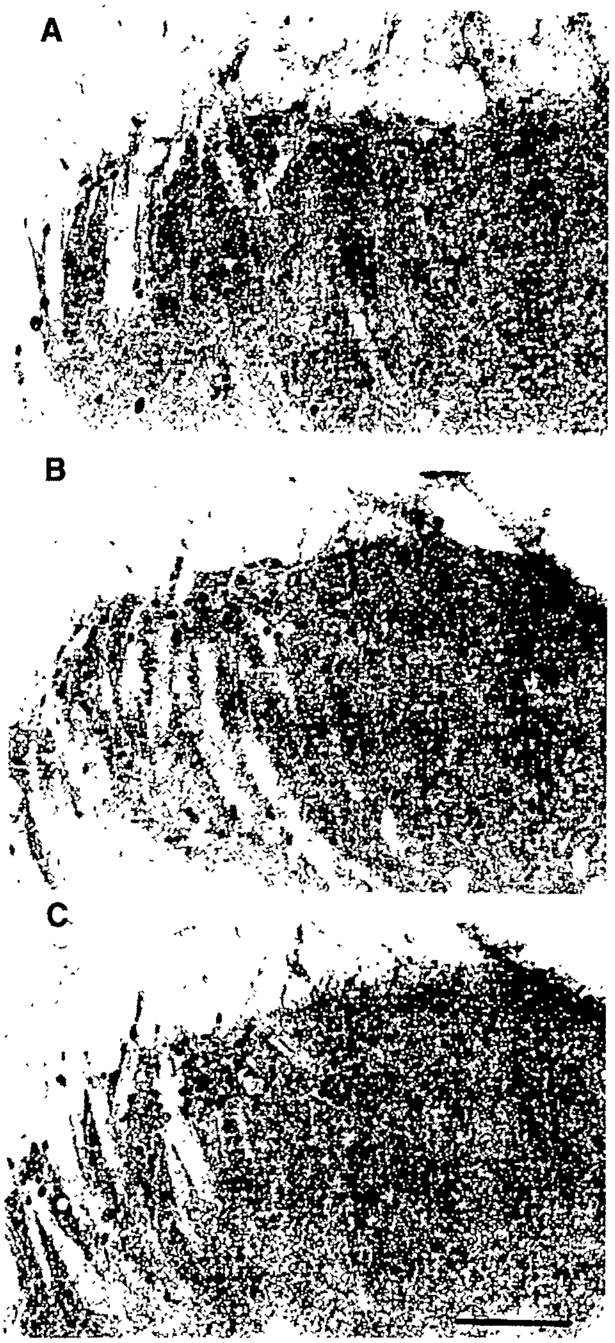

Figure 3 Microphotographs of superficial laminae of spinal dorsal horn showing reducing effects of intraplantar 0.5% bupivacaine and 2% lignocaine on the number of c-*fos* LI neurones, 1 h after intraplantar carrageenan in rats. Each microphotograph is an individual example, including labelled nuclei of c-*fos* LI neurones in superficial laminae (laminae I–II) per section (40 μm) of L4–L5 segments of the spinal cord; scale bar=100 μm. A = Control; B = 0.5% bupivacaine; C = 2% lignocaine.

at 60 min after carrageenan (fig. 4B,C, table 1). Therefore, intraplantar pre-administration of both bupivacaine and lignocaine had a similar effect on the number of superficial and deep c-*fos* LI neurones induced at 60 min after carrageenan (table 1).

In the bupivacaine group, a significant reduction in the total number of c-*fos* LI neurones induced at 180 min after intraplantar carrageenan was observed (29 (4)% reduction of control group values; $P < 0.01$) (fig. 4A, table 1). This effect resulted from a significant reduction in the number of deep c-*fos* LI neurones (31 (5) % reduction of control group values; $P < 0.001$) without effect on the superficial laminae (fig. 4B,C, table 1). In contrast, in the lignocaine group, the number of spinal c-*fos* LI neurones induced at 180 min after carrageenan was not affected (table 1).

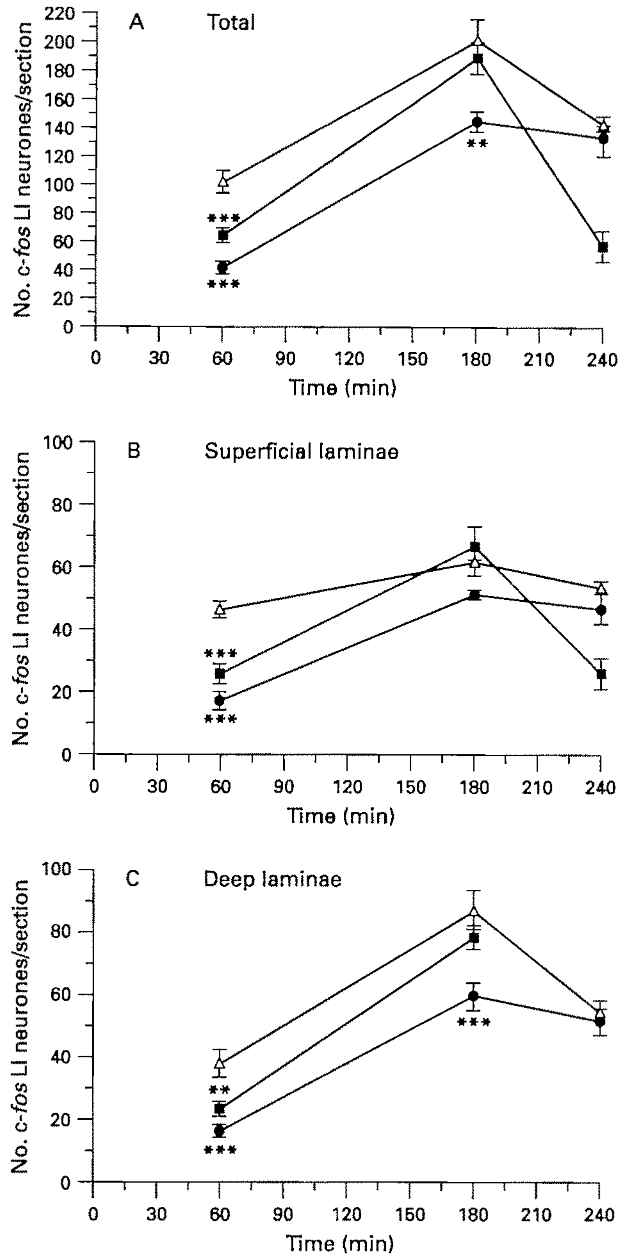

Figure 4 Effects of intraplantar 0.5% bupivacaine (●) and 2% lignocaine (■) on the number of c-*fos* LI neurones in the L4–L5 segments of the rat spinal cord at 1, 3 and 4 h after intraplantar carrageenan. Results are expressed as absolute mean (SEM) of (A) total number of carrageenan evoked c-*fos* LI neurones per section of segments L4–L5 and number of superficial (B) and deep (C) c-*fos* LI neurones per section for each region in the L4–L5 segments, 3 h after intraplantar carrageenan. Significance compared with control group (Δ) was performed using ANOVA and Fisher's PLSD test ($^{**}P < 0.01$, $^{***}P < 0.001$). The study of the effect of lignocaine at 4 h was not performed.

Intraplantar pre-administration of bupivacaine did not influence spinal c-*fos* expression induced at 240 min after carrageenan (table 1). As intraplantar lignocaine did not influence spinal c-*fos* expression at 180 min after carrageenan, the study of its effect at 240 min after carrageenan was not performed.

Discussion

Intraplantar administration of a long-acting local anaesthetic, bupivacaine, postponed mechanical allodynia and spinal c-*fos* protein expression associated with the inflammatory state induced by intraplantar injection of carrageenan in rats, while a short-acting local anaesthetic, lignocaine, reduced only transiently carrageenan-induced spinal c-*fos* protein expression. Overall, the effects of intraplantar bupivacaine and lignocaine in the carrageenan model of inflammatory pain were related to the duration of action of the anaesthetics.

TIME COURSE OF VOCALIZATION THRESHOLD AND OEDEMA

In accordance with previous studies (Kayser and Guilbaud[9], see references in Buritova and colleagues[19]) intraplantar injection of carrageenan induced ipsilateral oedema, without influencing the contralateral hind paw, at all times. The lack of effect of pre-administered intraplantar 2% lignocaine 200 μl on either oedema or VTPP after carrageenan was in concordance with previous studies showing the short duration of the antinociceptive effect of similar doses of lignocaine in behavioural experiments using the carrageenan model of inflammatory pain (18 min after 2% lignocaine 50 μl[9]) or formalin response in an orofacial pain model (6 min after 2% lignocaine 50 μl[23]).

In a carrageenan model of inflammatory pain, analgesia was defined previously as VTPP within the range of usual variability of the control value in normal situations (i.e. 85–115% of control value[9]). In this study, the duration of analgesic action of 0.5% bupivacaine 200 μl was estimated to be 55 (16) min after carrageenan. Similarly, pre-administered intraplantar bupivacaine reduced ankle oedema evoked at 60 min after carrageenan but this effect did not persist. The combined effect of bupivacaine on extension of oedema and reduction of VTPP may be related, at least in part, to the transient abolition of the axon reflex involved in the development and extension of inflammation[24]. The mechanism of action of bupivacaine involves binding of bupivacaine to voltage-dependent Na^+ channels which reduces neuronal transmission, axon reflex and consequently development of inflammation (see Butterworth and Strichartz[25] and references therein). In addition, local anaesthetics have been shown to block peripheral release of inflammatory substances such as substance P.[26] Thus the mechanisms mentioned above may be involved in the transient peripheral anti-inflammatory effect of intraplantar bupivacaine. The limited extent of peripheral oedema in the bupivacaine group, at 60 min after carrageenan, corresponded to the peripheral analgesic effect of bupivacaine during the period of its action. Overall, the peripheral effects of local anaesthetics probably reduced the nociceptive inputs and consequently influenced carrageenan-induced spinal c-*fos* expression.

TIME COURSE OF SPINAL C-*FOS* EXPRESSION

In the control group, spinal c-*fos* expression at 60, 180 and 240 min after intraplantar carrageenan was in agreement with our previous study showing the time course of spinal c-*fos* expression in the same model of inflammatory pain (see references in Buritova and colleagues[19]). This carrageenan evoked spinal c-*fos* expression was localized predominantly in the superficial (I–II) and deep (V–VI) laminae of the dorsal horn of the spinal cord in accordance with the spinal areas containing neurones activated by noxious stimuli driven by C- and Aδ-fibres[27] which evoked the spinal c-*fos* expression.[28]

Pre-administration of lignocaine attenuated spinal c-*fos* expression in both superficial and deep laminae at 60 min after carrageenan. This effect did not persist and the maximal number of c-*fos* neurones similar to the control group was reached at 180 min after carrageenan. This effect is in keeping with an electrophysiological study showing that administration of 2% lignocaine 50 μl s.c. into the site of peripheral injection of formalin completely blocked the first phase of the response to formalin of the deep dorsal horn neurones (about the first 10 min) without affecting second phase activity.[29] Thus 2% lignocaine 50–200 μl seems to be sufficient to prevent transmission of nociceptive inputs during the initial phase of nociceptive primary afferent activation with consequent attenuation of the time pattern of spinal c-*fos* expression. In this study, the reduced number of c-*fos* LI neurones at 60 min may reflect both a short duration of block of noxious input produced by lignocaine at the initial phase of inflammation and c-*fos* protein synthesis delay related to delay of c-*fos* messenger RNA (mRNA) expression about 30 min after carrageenan.[30]

In the bupivacaine group, the reduction in spinal c-*fos* expression in both superficial and deep laminae was observed 60 min after carrageenan. At 180 min after carrageenan when the reduction in VTPP, reflecting mechanical allodynia, was equivalent to control group values, c-*fos* expression in the superficial laminae was similar to the control group. However, at this time the total number of c-*fos* LI neurones and c-*fos* expression in deep laminae were lower than in the control group. This laminar pattern is not surprising as c-*fos* protein is initially expressed in superficial neurones, and subsequently in the neurones in the deep laminae of the spinal dorsal horn at a later phase of noxious stimulus transmission, as has been shown after intraplantar injection of formalin[31] and carrageenan.[12 17] Thus, in this study, the laminar pattern of carrageenan-induced spinal c-*fos* expression, influenced by intraplantar administration of both bupivacaine and lignocaine, may result from peripheral block of nociceptive input by local anaesthetics and consequently delayed c-*fos* expression at the spinal cord level.

Interestingly, the effect of pre-administered intraplantar bupivacaine on the laminar pattern of carrageenan-induced spinal c-*fos* expression at 60 min after carrageenan was similar to that observed with pre-administered intraplantar morphine[18] and various systemic NSAID (see references in Buritova and colleagues[19]) observed previously in the same experimental paradigm at 180 min after carrageenan. In these previous studies, the period of 180 min after intraplantar carrageenan had been covered by activity of the analgesic/anti-inflammatory drugs which resulted in reduction of c-*fos* expression in both superficial and deep laminae of the spinal dorsal horn. Overall, during the period of drug activity, both bupivacaine (60 min after carrageenan) and analgesic/anti-inflammatory drugs (180 min after carrageenan (see references in Buritova and colleagues[19]) had a similar effect on reducing spinal c-*fos* expression in both superficial and deep laminae. In contrast, after the period of drug activity (e.g. at 180 min after carrageenan), administration of bupivacaine induced a dissociative laminar pattern of spinal c-*fos* expression without effect on c-*fos* expression in superficial laminae. This dissociative effect of bupivacaine was similar to that described previously with the NMDA receptor antagonist, ($^+$)-HA966, in the same experimental paradigm.[32] Interestingly, bupivacaine and ($^+$)-HA 966[33] have a similar duration of antinociceptive effect (about 60 min).

In this study, the absence of persistent effects of intraplantar local anaesthetic on both behavioural nociceptive test and spinal c-*fos* expression in the superficial laminae does not support the hypothesis of efficacy of pre-emptive analgesia. However, the reduction in both total and deep laminae c-*fos* expression by bupivacaine may have an influence on the development of chronic pain states but additional studies are required to test this hypothesis.

LOCAL ANAESTHETICS AND PREVENTION OF PAIN

In this study we used parallel behavioural and immunohistochemical approaches to assess the possible pre-emptive effect of local anaesthetics. The reduction in spinal c-*fos* expression in both the superficial and deep laminae at 60 min suggests that local anaesthetic pre-infiltration interrupted nociceptive inputs during the initial phase of carrageenan inflammation. However, a longer block may be necessary to reveal a pre-emptive analgesic effect of local anaesthetics. Thus an increase in the dose of local anaesthetic used for infiltration or a nerve block technique may be proposed. Unfortunately, re-injection in this study would have been toxic (1 mg of bupivacaine was already injected; i.e. more than 4 mg kg^{-1}). Furthermore, we have previously used 0.5% bupivacaine with adrenaline or higher doses (5 mg of bupivacaine instead of 1 mg in 200 μl) of bupivacaine included in microspheres[34] which produced, respectively, a 100%[21] and 175% (unpublished data) increase in analgesia related to infiltration but without a pre-emptive effect detected by behavioural tests in the same carrageenan model. In contrast, the intervention required for nerve block may induce additional nociceptive stimulation which influences carrageenan-induced spinal c-*fos* expression and consequently impairs the homogeneity of control values. In addition, the behavioural test used in this study (vocalization threshold to paw pressure) may be difficult to evaluate when there is total paralysis of the limb.

The development of inflammatory nociception induced by intraplantar carrageenan in the rat is comparable to the time course of postoperative pain (24–96 h) and it might explain the similar results of this study and clinical studies on pre-emptive analgesia with local anaesthetic infiltration of the site of superficial surgery (see references in Dahl and Kehlet[5]). Our results extend clinical studies showing that pre-emptive anaesthesia with infiltration by local anaesthetics has no long-term benefits for postoperative analgesia (see references in Dahl and Kehlet[5]).

In summary, the effects of intraplantar pre-administration of bupivacaine and lignocaine on carrageenan-induced mechanical allodynia did not persist beyond the direct local anaesthetic effect. Similarly, carrageenan-induced nociceptive inputs were reduced only briefly by local anaesthetics, as shown by the transient reduction in spinal c-*fos* expression, an indicator of nociceptive transmission at the spinal cord.

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References

1. Bonica JJ, Butler SH. Local anaesthesia and regional blocks. In: Wall PD, Melzack R, eds. *Texbook of Pain*. Edinburgh: Churchill Livingstone, 1994; 997–1023.
2. Wall PD. The prevention of postoperative pain. *Pain* 1988; 33: 289–290.
3. McQuay HJ. Do preemptive treatments provide better pain control?. In: Gebhart GF, Hammond DL, Jensen TS, eds. *Proceedings of the 7th World Congress on Pain, Progress in Pain Research and Management, Vol. 2.* Seattle: IASP Press, 1994; 709–723.
4. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; 52: 259–285.
5. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. *British Journal of Anaesthesia* 1993; 70: 434–439.
6. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesthesia and Analgesia* 1993; 77: 362–379.
7. Winter CA, Risley EA, Nuss GW. Carrageenan-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. *Proceedings of the Society for Experimental Biology and Medicine* 1962; 111: 544–547.
8. Kocher L, Anton F, Reeh PW, Handwerker HO. The effect of carrageenin-induced inflammation on the sensitivity of unmyelinated skin nociceptors in the rat. *Pain* 1987; 29: 363–373.
9. Kayser V, Guilbaud G. Local and remote modifications of nociceptive sensitivity during carrageenan-induced inflammation in the rat. *Pain* 1987; 28: 99–107.
10. Noguchi K, Kowalski K, Traub R, Solodkin A, Iadarola MJ, Ruda MA. Dynorphin expression and fos-like immunoreactivity following inflammation induced hyperalgesia are colocalized in spinal cord neurons. *Molecular Brain Research* 1991; 10: 227–233.

11. Noguchi K, Dubner R, Ruda MA. Preproenkephalin mRNA in spinal dorsal horn neurons is induced by peripheral inflammation and is co-localized with fos and fos-related proteins. *Neuroscience* 1992; **46**: 561–570.
12. Honoré P, Buritova J, Besson JM. Carrageenin-evoked c-*fos* expression in rat lumbar spinal cord: the effects of indomethacin. *European Journal of Pharmacology* 1995; **272**: 249–259.
13. Morgan JI, Curran T. Immediate-early genes: ten years on. *Trends in Neuroscience* 1995; **18**: 66–67.
14. Hughes P, Dragunow M. Induction of immediate-early genes and the control of neurotransmitter-regulated expression within the nervous system. *Pharmacological Reviews* 1995; **47**: 133–178.
15. Hunt SP, Pini A, Evan G. Induction of c-*fos*-like protein in spinal cord neurones following sensory stimulation. *Nature (London)* 1987; **328**: 632–634.
16. Zimmermann M, Herdegen T. Control of gene transcription by jun and fos proteins in the nervous system *APS Journal* 1994; **3**: 33–62.
17. Honoré P, Chapman V, Buritova J, Besson JM. When is the maximal effect of pre- administered systemic morphine on carrageenin evoked spinal c-fos expression in the rat? *Brain Research* 1995; **705**: 91–96.
18. Honoré P, Buritova J, Besson JM. Intraplantar morphine depresses spinal c-fos expression induced by carrageenin inflammation but not by noxious heat. *British Journal of Pharmacology* 1996; **118**: 671–680.
19. Buritova J, Honoré P, Chapman V, Besson JM. Enhanced effects of co-administerd dexamethasone and diclofenac on inflammatory pain processing and associated spinal c-fos expression in the rat. *Pain* 1996; **64**: 559–568.
20. Zimmermann M. Ethical guidelines for investigations of experimental pain in conscious animals. *Pain* 1983; **16**: 109–110.
21. Fletcher D, Kayser V, Guilbaud G. Evaluation of the pre-emptive analgesic effect of bupivacaine in carrageenin injected rats. *European Journal of Neuroscience* 199.
22. Kayser V, Guilbaud G. Differential effects of various doses of morphine and naloxone on two nociceptive test thresholds in arthritic and normal rats. *Pain* 1990; **41**: 353–363.
23. Dallel R, Raboisson P, Clavelou P, Saade M, Woda A. Evidence for a peripheral origin of the tonic nociceptive response to subcutaneous formalin. *Pain* 1995; **61**: 11–16.
24. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. In: Melzack R, Wall PD, eds. *Text Book of Pain*. Edinburgh: Churchill Livingstone, 1994; 13–44.
25. Butterworth JF, Strichartz GR. Molecular mechanisms of local anesthesia: A review. *Anesthesiology* 1990; **72**: 711–734.
26. Hart R, Dancygier H, Wagner F, Niedermeyer H, Classen M. Substance P modulates lymphokine activities in supernatants of cultured human duodenal biopsies. *Immunology Letters* 1988; **19**: 133–136.
27. Besson JM, Chaouch A. Peripheral and spinal mechanisms of nociception. *Physiological Reviews* 1987; **67**: 67–186.
28. Herdegen T, Kovary K, Leah J, Bravo R. Specific temporal and spatial distribution of JUN, FOS and KROX-24 proteins in spinal neurons following noxious transsynaptic stimulation. *Journal of Comparative Neurology* 1991; **313**: 178–191.
29. Haley JE, Sullivan AF, Dickenson AH. Evidence for spinal *N*-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. *Brain Research* 1990; **518**: 218–226.
30. Draisci G, Iadarola MJ. Temporal analysis of increases in c-*fos*, preprodynorphin and preproenkephalin mRNAs in rat spinal cord. *Molecular Brain Research* 1989; **6**: 31–37.
31. Presley RW, Menétrey D, Levine JD, Basbaum AI. Systemic morphine suppresses noxious stimulus-evoked fos protein-like immunoreactivity in the rat spinal cord. *Journal of Neuroscience* 1990; **10**: 323–335.
32. Chapman V, Honoré P, Buritova J, Besson JM. The contribution of NMDA receptor activation to spinal c-fos expression in a model of inflammatory pain. *British Journal of Pharmacology* 1995; **116**: 1628–1634.
33. Millan MJ, Seguin L. ($^{+}$)-HA966, a partial agonist at the glycine site coupled to NMDA receptors, blocks formalin-induced pain in mice. *European Journal of Pharmacology* 1993; **238**: 445–447.
34. Le Corre P, Estebe JP, Chevanne F, Malledant Y, Le Verge R. Spinal controlled delivery of bupivacaine from lactic acid oligomer microspheres. *Journal of Pharmaceutical Sciences* 1995; **84**: 75–78.

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Myocardial effects of eltanolone in hamsters with hypertrophic cardiomyopathy

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Summary

Eltanolone is a new short-acting i.v. induction agent that induces less cardiovascular depression than propofol or thiopentone and has no significant effect on intrinsic contractility in normal myocardium. However, its effects on diseased myocardium are unknown. We have studied *in vitro* the effects of eltanolone 0.1, 1, and 10 $\mu g\ ml^{-1}$ on the intrinsic contractility of left ventricular papillary muscles from normal hamsters and those with hypertrophic cardiomyopathy (strain BIO 14.6, 6-month-old) (Krebs–Henseleit solution, 29 °C, pH 7.40, Ca^{2+} 2.5 mmol $litre^{-1}$, stimulation frequency 3 min^{-1}). Cardiac hypertrophy (mean 134 (SD 9) %, $P < 0.001$) was observed in cardiomyopathic hamsters. Contractility of papillary muscles from hamsters with cardiomyopathy was less than that of controls, as shown by the lower active isometric force (8 (3) *vs* 35 (14) mN mm^{-2}, $P < 0.001$). Eltanolone did not induce any significant inotropic or lusitropic effects in normal hamsters, and the effects of eltanolone were not significantly different between normal hamsters and those with cardiomyopathy.(*Br. J. Anaesth.* 1996; **77**: 653–657)

Key words
Anaesthetics i.v., eltanolone. Heart, cardiomyopathy. Heart, myocardial function. Heart, inotropism. Hamster.

Eltanolone is a new short-acting i.v. anaesthetic agent which has undergone preliminary clinical investigation.[1–3] Eltanolone (3α-hydroxy-5β-pregnan-20-one) is a naturally occurring metabolite of progesterone which has been shown to be 3.2 times more potent than propofol and six times more potent than thiopentone.[3] The decrease in arterial pressure produced by eltanolone has been shown to be smaller than that after an equipotent dose of propofol.[3]

Because of concomitant changes in preload, systemic resistance, sympathetic activity and central nervous system activity, the exact effects of anaesthetic agents on intrinsic myocardial contractility are difficult to assess *in vivo*.[4] *In vitro*, eltanolone has been shown to induce no significant inotropic effect on rat myocardium.[5] Nevertheless, eltanolone induced a decrease in the calcium release function of the sarcoplasmic reticulum.[5]

The effects of eltanolone on diseased myocardium are unknown. It has been demonstrated that the myocardial effects of anaesthetic agents may differ between normal and diseased myocardium.[6 7] The various strains of Syrian hamsters with hereditary cardiomyopathy offer an opportunity to investigate the effects of anaesthetic agents on intrinsic myocardial contractility. Contractility, cellular biochemistry, molecular biology and pathophysiology have been studied extensively in the model, and impairment in contractility is caused primarily by cardiac muscle cell disease, and thus may be more relevant to clinical cardiomyopathies.[8 9] We therefore conducted an *in vitro* study of the effects of eltanolone on intrinsic contractility of left ventricular papillary muscle from normal hamsters and those with cardiomyopathy.

Materials and methods

Care of the animals conformed to the recommendations of the Helsinski Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture. We studied eight normal Syrian hamsters (strain F1B) and 13 cardiomyopathic Syrian hamsters (strain BIO 14.6) (Bio Breeders Inc., Fitchburg, MA, USA). In this strain, all animals of both sexes develop hypertrophic cardiomyopathy from the age of 6 weeks. All animals were aged 6 months. Body weight (BW) and heart weight (HW) were determined at the moment of killing and the HW/BW ratio was calculated. Cardiac hypertrophy index was calculated by dividing the HW/BW value of each cardiomyopathic hamster by the mean HW/BW value in normal hamsters.

We studied 21 left ventricular papillary muscles. After brief anaesthesia with ether, the hearts were removed rapidly and left ventricular papillary

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muscles were excised carefully and suspended vertically in a 200-ml jacketed reservoir with Krebs–Henseleit bicarbonate buffer solution containing (mmol litre^{-1}): NaCl 118, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.1, $NaHCO_3$ 25, $CaCl_2$ 2.5 and glucose 4.5 . The Krebs–Henseleit solution was prepared daily with highly purified water (Ecopure, Barnstead/Thermolyne Corporation, Dubuque, IA). The jacketed reservoir was maintained at 29 °C with a thermostatic water circulator (Polystat 5HP, Bioblock, Illkirch, France) and continuous monitoring of the solution temperature with a temperature probe (Pt100, Bioblock). Preparations were field-stimulated at 3 pulses min^{-1} by two platinum electrodes with rectangular wave pulses of 5-ms duration just above threshold. The bathing solution was bubbled with 95% oxygen–5% carbon dioxide, resulting in a pH of 7.40. After a 90-min stabilization period at the initial muscle length at the apex of the length-active isometric tension curve (*l*max), papillary muscles recovered their optimal mechanical performance, which remained stable for many hours.

The pharmaceutical form of eltanolone in which a soya bean emulsion is the solvent (Pharmacia, Stockholm, Sweden) was tested. The solvent has been shown to be devoid of significant effects on intrinsic myocardial contractility.[5,10,11] Concentrations of eltanolone during anaesthesia range from 0.3 to 3 μg ml^{-1}.[12] Eltanolone is highly bound (99%) to plasma proteins,[13] but this does not seem to influence its rapid disappearance from blood and extensive tissue distribution. Thus three concentrations of eltanolone were tested in a cumulative manner: 0.1 μg ml^{-1} (0.31 μmol litre^{-1}), 1 μg ml^{-1} (3.14 μmol litre^{-1}) and 10 μg ml^{-1} (31.4 μmol litre^{-1}), with a lapse of 15 min between each dose, as reported previously in rat myocardium.[5]

ELECTROMAGNETIC LEVER SYSTEM AND RECORDING

The electromagnetic lever system has been described previously.[14] Briefly, the load applied to the muscle was determined by means of a Servo mechanism-controlled current through the coil of an electromagnet. Muscular shortening induced displacement of the lever, which modulated the light intensity of a photoelectric transducer. All analyses were made from digital records of force and length obtained with a computer, as described previously.[15]

MECHANICAL VARIABLES

Conventional mechanical variables at *l*max were calculated from three twitches. The first twitch was isotonic and was loaded with the preload corresponding to *l*max. The second twitch was clamped abruptly to zero load just after the electrical stimulus; the muscle was released from preload to zero load with a critical damping in order to slow the first and rapid shortening overshoot resulting from recoil of series passive elastic components, as reported previously[16]; maximum unloaded shortening velocity (*v*max) was determined from this twitch. The third twitch was fully isometric at *l*max. The mechanical variables characterizing the contraction and relaxation phases, and the coupling between contraction and relaxation were defined as follows.

Contraction phase

We determined *v*max using the zero load clamp technique: maximum shortening velocity ($v_c$max) of the twitch with preload only; maximum isometric active force normalized per cross-sectional area (AF); and peak of the positive force derivative normalized per cross-sectional area (+d*F*. d*t*$^{-1}$). *v*max and AF tested the inotropic state under low and high loads, respectively.

Relaxation phase

We determined maximum lengthening velocity of the twitch with preload only ($v_r$max) and the peak of the negative force derivative at *l*max normalized per cross-sectional area (−d*F*. d*t*$^{-1}$). These two variables examined relaxation under low- and high-loading conditions, respectively. Nevertheless, as changes in the contraction phase induce coordinated changes in the relaxation phase, $v_r$max and −d*F*. d*t*$^{-1}$ cannot assess lusitropy, and thus variations in contraction and relaxation must be considered simultaneously to quantify drug-induced changes in lusitropy. Indices of contraction–relaxation coupling have therefore been developed to study lusitropy.[17]

Contraction–relaxation coupling

Coefficient R1 = $v_c$max/$v_r$max examined the coupling between contraction and relaxation under low load, and thus lusitropy. Under isotonic conditions the amplitude of sarcomere shortening is twice that observed under isometric conditions.[18] Because of the lower sensitivity of myofilament for calcium when cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently as a result of rapid uptake of calcium by the sarcoplasmic reticulum (SR). Thus R1 tests SR function. In contrast with $v_c$max and $v_r$max, R1 is not modified significantly by major inotropic changes induced by decreasing calcium.

Coefficient R2 = (+d*F*. d*t*$^{-1}$/−d*F*. d*t*$^{-1}$) studied the coupling between contraction and relaxation under high load, and thus lusitropy under high load. When the muscle contracts isometrically, sarcomeres shorten very little.[18] Because of the higher sensitivity of myofilament for calcium,[19] the relaxation time course is determined by calcium unbinding from troponin C rather than by calcium sequestration by the SR. Thus R2 reflects myofilament calcium sensitivity. The variables R1 and R2 which examine lusitropy have been used empirically for many years, but have been validated recently.[20,21]

At the end of the study, muscle cross-sectional area was calculated from the length and weight of papillary muscle, assuming a density of 1. Shortening and lengthening velocities were expressed in *l*max s^{-1}, force in mN mm^{-2} and force derivative in mN mm^{-2} s^{-1}.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). Control values in normal hamsters and those with cardiomyopathy were compared using the Student's *t* test. The effects of eltanolone in normal hamsters and in those with cardiomyopathy were compared by repeated-measures analysis of variance and the Newman–Keuls test. All P values were two-tailed, and $P < 0.05$ was required to reject the null hypothesis.

Results

Heart weight (HW) was not significantly different between normal hamsters and those with cardiomyopathy. However, the HW/BW ratio was significantly greater in cardiomyopathic hamsters, indicating marked cardiac hypertrophy (table 1). The intrinsic mechanical performance of papillary muscles from hamsters with cardiomyopathy was significantly lower during isometric (AF) and isotonic (*v*max) twitches (table 2, fig. 1). R1 and R2, which test lusitropy under low and high load, were not significantly different between the two groups.

Eltanolone induced no significant inotropic effect on normal muscles, as shown by the absence of changes in *v*max and AF (table 3). There were no differences in these inotropic variables between normal hamsters and those with cardiomyopathy (table 3). Under isotonic conditions, eltanolone had no significant lusitropic effect (R1), and there were no significant differences between normal hamsters and those with cardiomyopathy (table 3). Under isometric conditions, eltanolone had no significant lusitropic effect (R2) in normal hamsters, and no significant differences were noted between normal hamsters and those with cardiomyopathy (table 3).

Table 1 Characteristics of normal hamsters ($n = 8$) and those with cardiomyopathy ($n = 13$) (mean (SD)). BW = Body weight; HW = heart weight. Cardiac hypertrophy index was determined by dividing the HW/BW value of each cardiomyopathic hamster by the mean HW/BW value of normal hamsters. $^*P < 0.05$ *vs* normal hamsters

Variable	Normal hamsters	Cardiomyopathic hamsters
BW (g)	147 (5)	102 (9) *
HW (mg)	429 (21)	440 (54)
HW/BW (10^{-3})	3.2 (0.1)	4.3 (0.3) *
Cardiac hypertrophy index (%)	100	134 (9) *

Table 2 Characteristics of left ventricular papillary muscles from normal hamsters ($n = 8$) and those with cardiomyopathy ($n = 13$) (mean (SD)). *l*max = Initial length; CSA = cross-sectional area; RF/TF = ratio of resting force to total force; *v*max = maximum unloaded shortening velocity; AF = isometric active force normalized per CSA; R1 = contraction–relaxation coupling under low load; R2 = contraction–relaxation coupling under high load. $^*P < 0.05$ *vs* normal hamsters

Variable	Normal hamsters	Cardiomyopathic hamsters
*l*max (mm)	4.0 (0.8)	3.2 (0.7)*
CSA (mm^2)	0.89 (0.17)	0.89 (0.15)
RF/TF	0.15 (0.05)	0.20 (0.05)*
*v*max (*l*max s^{-1})	3.10 (0.50)	2.57 (0.53)*
AF (mN mm^{-2})	35 (14)	8 (3)*
R1	0.94 (0.12)	1.02 (0.14)
R2	1.57 (0.13)	1.47 (0.19)

Discussion

We have observed that eltanolone induced no significant effects on the intrinsic mechanical properties of left ventricular papillary muscles from normal hamsters, and that there were no significant differences in the effects of eltanolone in normal hamsters and those with cardiomyopathy.

Eltanolone did not modify contraction–relaxation coupling under low load (Rl). Under isotonic conditions, the amplitude of sarcomere shortening is twice that observed under isometric conditions,[18] and the time course of isotonic relaxation occurs earlier and more rapidly than that of isometric relaxation, partly via two mechanisms[19]: (1) easier removal of calcium from troponin C caused by a decrease in myofilament calcium sensitivity; and (2) rapid uptake of calcium by the SR. Under low load, the SR appears to

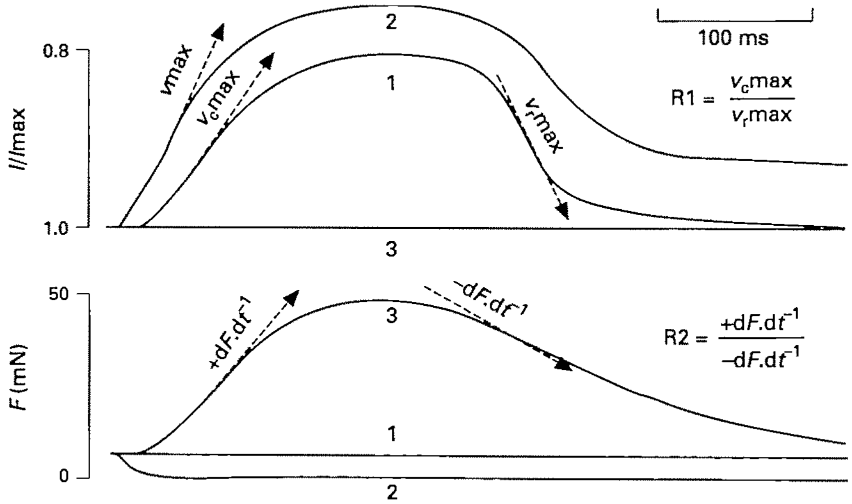

Figure 1 Mechanical variables of contraction and relaxation. Top: Muscle shortening length (*l*/*l*max) *vs* time. Bottom: Force (*F*) *vs* time. Twitch 1 was loaded with preload only at *l*max. Twitch 2 was loaded with the same preload as twitch 1 and was abruptly clamped to zero load just after the electrical stimulus. Twitch 3 was fully isometric.

Table 3 Comparison of the effects of eltanolone on left ventricular papillary muscles from normal ($n = 8$) and cardiomyopathic hamsters ($n = 13$). *v*max = Maximum unloaded shortening velocity; AF = isometric active force normalized per CSA; R1 = contraction–relaxation coupling under low load; R2 = contraction–relaxation coupling under high load. Values are mean (SD) percentage of control values. No significant differences between groups

		Eltanolone concentration (μg ml^{-1})		
Mechanical variables	Group	0.1	1	10
Inotropy				
*v*max(*l*max s^{-1})	Normal	117 (17)	119 (17)	116 (22)
	Cardiomyopathic	107 (9)	106 (12)	107 (13)
AF (mN mm^{-2})	Normal	113 (13)	113 (13)	109 (19)
	Cardiomyopathic	107 (11)	112 (15)	112 (16)
Lusitropy				
R1	Normal	102 (3)	97 (11)	99 (11)
	Cardiomyopathic	100 (4)	103 (5)	102 (5)
R2	Normal	105 (7)	102 (8)	101 (8)
	Cardiomyopathic	98 (6)	100 (5)	100 (6)

play a major role in the regulation of isotonic relaxation. Therefore, our results suggest that eltanolone did not modify uptake of calcium by the SR. This result agrees with that obtained previously in rat myocardium.[5]

Contraction–relaxation coupling under high load (R2) was not modified by eltanolone. Under isometric conditions and because of slight sarcomere shortening, myofilament calcium sensitivity is decreased less than under isotonic conditions and becomes the limiting step that appears to play a major role in the regulation of the time course of isometric relaxation. The absence of any lusitropic effect of eltanolone under high load suggests that it did not modify myofilament calcium sensitivity, as reported previously in rat myocardium.[5]

Genetically induced cardiomyopathy in Syrian hamsters is characterized by progressive occurrence of focal myocardial degeneration, fibrosis and calcifications during the life of the animal.[8 9] At age 30–40 days, histological lesions become apparent and myocardial performance decreases. Additional cardiac changes include hypertrophy, or dilatation, or both, depending on the strain, then congestive heart failure and death. In our study, myocardial contractility was impaired markedly in cardiomyopathic muscles, as reflected by the decrease in *v*max and AF (table 2). Decreased myocardial contractility in cardiomyopathic hamsters may be explained by decreased activity of G proteins,[22] decreased sarcolemmal Ca^{2+} and Na^+–K^+ ATPase activities,[23] alterations in Na–Ca exchange,[24] decreased conductance and density of voltage-sensitive calcium channels,[25] alterations in the creatine kinase system,[26] and alteration in myofilament regulatory proteins.[27] Nevertheless, a decrease in SR function is not observed in all strains, and the strain used in our study (BIO 14.6) which develops hypertrophic cardiomyopathy has been shown to exhibit normal SR function.[28] In this study, the lack of significant increase in R1 is consistent with these results and concords with results obtained previously in other strains with hypertrophic cardiomyopathy.[29]

Because of the complex action of anaesthetic agents on cardiac muscle and because of the various pathological changes observed in the myocardium of cardiomyopathic hamsters, it is not easy to predict the mechanical effects of anaesthetic agents on this diseased myocardium. Indeed, it has been demonstrated that the mechanical effects of ketamine[6] and etomidate[7] differ in normal and cardiomyopathic hamsters. In contrast, in this study, we observed that the mechanical effects of eltanolone did not differ in left ventricular papillary muscles from normal and cardiomyopathic hamsters.

The following points must be considered in the assessment of the clinical relevance of our results. First, because this study was conducted *in vitro*, it dealt only with intrinsic myocardial contractility. Observed changes in cardiac function after *in vivo* administration of eltanolone also depend on modifications in venous return, afterload and compensatory mechanisms. This point should be of special importance in patients with cardiomyopathy whose cardiac function depends not only on intrinsic contractility but also on preload, postload and sympathetic activity. Second, this study was conducted at 29 °C and at a low stimulation frequency; however, papillary muscles must be studied at this temperature because stability of mechanical variables is not sufficient at 37 °C and at a low frequency because high stimulation frequency induces core hypoxia.[30] Moreover, higher stimulation rates frequently induce extrasystoles in cardiomyopathic muscles, resulting in an unreliable recording of mechanical variables. Third, this study was performed on hamster myocardium, which differs from human myocardium. Furthermore, because eltanolone is highly bound to plasma proteins[13] and because the bathing solution was protein-free, the concentrations tested might be considered high.

In summary, in studies conducted on isolated left ventricular papillary muscle, eltanolone did not modify intrinsic myocardial contractility in normal hamsters, and no significant differences were observed between normal and cardiomyopathic hamsters. These results could be important as most anaesthetic agents decrease myocardial contractility.[31]

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References

1. Gray H St J, Holt BL, Whitaker DK, Eadsforth P. Preliminary study of a pregnanolone emulsion (Kabi 2213) for i.v. induction of general anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 272–276.
2. Powell H, Morgan M, Sear JW. Pregnanolone: a new steroid intravenous anaesthetic. Dose-finding study. *Anaesthesia* 1992; 47: 287–290.
3. Van Hemelrijck J, Muller P, Van Aken H, White PF. Relative potency of eltanolone, propofol, and thiopental for induction of anesthesia. *Anesthesiology* 1994; **80**: 36–41.
4. Vatner SF. Effects of anesthesia on cardiovascular control mechanisms. *Environmental Health Perspectives* 1978; **26**: 193–206.
5. Riou B, Ruel P, Hanouz JL, Langeron O, Lecarpentier Y, Viars P. In vitro effects of eltanolone on rat myocardium. *Anesthesiology* 1995; **83**: 792–798.
6. Riou B, Viars P, Lecarpentier Y. Effects of ketamine on the cardiac papillary muscle of normal hamsters and those with cardiomyopathy. *Anesthesiology* 1990; **73**: 910–918.
7. Riou B, Lecarpentier Y, Viars P. Effects of etomidate on the cardiac papillary muscle of normal hamsters and those with cardiomyopathy. *Anesthesiology* 1993; **78**: 83–90.
8. Bajusz E. Hereditary cardiomyopathy: A new disease model. *American Heart Journal* 1969; 77: 686–696.
9. Strobeck JE, Factor SM, Bahn A, Sole M, Liew CC, Fein F, Sonnenblick EH. Hereditary and acquired cardiomyopathies in experimental animals: Mechanical, biochemical, and structural features. *Annals of the New York Academy of Sciences* 1979; **317**: 59–88.
10. Riou B, Besse S, Lecarpentier Y, Viars P. *In vitro* effects of propofol on rat myocardium. *Anesthesiology* 1992; **76**: 609–616.
11. Riou B, Lejay M, Lecarpentier Y, Viars P. Myocardial effects of propofol in hamsters with hypertrophic cardiomyopathy. *Anesthesiology* 1995; **82**: 566–573.
12. Carl P, Hogskilde S, Lang-Jensen T, Bach V, Jacobsen J, Sorensen MB, Grälls M, Widlund L. Pharmacokinetics and pharmacodynamics of eltanolone (pregnanolone), a new steroid intravenous anaesthetic, in humans. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 734–741.
13. Grälls M, Nimmo W, Watson N. Pharmacokinetics of eltanolone after i.v. bolus injection in elderly patients. *British Journal of Anaesthesia* 1996; 76 (Suppl. 2): 90.
14. Lecarpentier Y, Martin JL, Gastineau P, Hatt PY. Load dependence of mammalian heart relaxation during cardiac hypertrophy and heart failure. *American Journal of Physiology* 1982; **242**: H855–861.
15. Riou B, Lecarpentier Y, Viars P. Inotropic effect of ketamine on rat cardiac papillary muscle. *Anesthesiology* 1989; **71**: 116–125.
16. Brutsaert DL, Claes VA. Onset of mechanical activation of mammalian heart muscle in calcium- and strontium-containing solutions. *Circulation Research* 1974; **35**: 345–347.
17. Chemla D, Lecarpentier Y, Martin JL, Clergue M, Antonetti A, Hatt PY. Relationship between inotropy and relaxation in rat myocardium. *American Journal of Physiology* 1986; **250**: H1008–1016.
18. Lecarpentier YC, Martin JL, Claes V, Chambaret JP, Migus A, Antonetti A, Hatt PY. Real-time kinetics of sarcomere relaxation by laser diffraction. *Circulation Research* 1985; **56**: 331–339.
19. Housmans PR, Lee NKM, Blinks JR. Active shortening retards the decline of intracellular calcium transient in mammalian heart muscle. *Science* 1983; **221**: 159–161.
20. Nwasokwa ON, Bodenheimer MM. Analysis of myocardial isometric dynamics using parameters of a global model. *American Journal of Physiology* 1989; **257**: H1275–1286.
21. Nwasokwa ON. A model of the time course of myocardial relaxation dynamics: use in characterisation of relaxation and evaluation of its indices. *Cardiovascular Research* 1993; **27**: 1510–1521.
22. Kessler PD, Cates AE, Van Dop C, Feldman AM. Decreased bioactivity of the guanine nucleotide-binding protein that stimulates adenylate cyclase in hearts from cardiomyopathic Syrian hamsters. *Journal of Clinical Investigation* 1989; **84**: 244–252.
23. Panagia V, Singh JN, Anand-Svristava MB, Pierce GN, Jasmin G, Dhalla NS. Sarcolemmal alterations during the development of genetically determined cardiomyopathy. *Cardiovascular Research* 1984; **18**: 567–572.
24. Wagner JA, Weisman HF, Snowman AM, Reynolds IJ, Weisfeldt ML, Snyder SH. Alterations in calcium antagonist receptors and sodium–calcium exchange in cardiomyopathic hamster tissues. *Circulation Research* 1989; **65**: 205–214.
25. Rossner KL. Calcium current in congestive heart failure of hamster cardiomyopathy. *American Journal of Physiology* 1991; **260**: H1179–1186.
26. Veksler VI, Ventura-Clapier R, Lechêne P, Vassort G. Functionnal state of myofibrils, mitochondria and bound creatine kinase in skinned ventricular fibers of cardiomyopathic hamsters. *Journal of Molecular and Cellular Cardiology* 1988; **20**: 329–342.
27. Malhotra A. Regulatory proteins in hamster cardiomyopathy. *Circulation Research* 1990; **66**: 1302–1309.
28. Whitmer JT, Kumar P, Solaro RJ. Calcium transport properties of cardiac sarcoplasmic reticulum from cardiomyopathic Syrian hamsters (BIO 53.58 and 14.6): Evidence for a quantitative defect in dilated myopathic hearts not evident in hypertrophied hearts. *Circulation Research* 1988; **62**: 81–85.
29. Antony I, Chemla D, Lecarpentier Y. Myocardial contractility, lusitropy and calcium responsiveness in young (50 days) and hypertrophied (180 days) cardiomyopathic hamsters. *Journal of Molecular and Cellular Cardiology* 1992; **24**: 1089–1100.
30. Paradise NF, Schmitter JL, Surmitis JM. Criteria for adequate oxygenation of isometric kitten papillary muscle. *American Journal of Physiology* 1981; **241**: H348–353.
31. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: A review of possible mechanisms. *Anesthesiology* 1987; **67**: 745–766.

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Comparison of the effects of controlled ventilation with 100% oxygen, 50% oxygen in nitrogen, and 50% oxygen in nitrous oxide on responses to venous air embolism in pigs

J. KYTTÄ, P. TANSKANEN AND T. RANDELL

Summary

In this randomized, experimental study in 18 pigs, we have investigated the effects of inspiratory air in oxygen, 100% oxygen and 50% nitrous oxide in oxygen on the detection and consequences of venous air embolism. Each animal was tested with injections of 1.0 ml kg^{-1} and 2.0 ml kg^{-1} of air. All animals, except one in the nitrous oxide group, survived the air emboli. Systolic and diastolic arterial pressures decreased significantly in all groups after both injections of air. Pulmonary diastolic pressures increased most in the nitrous oxide group. End-tidal concentration of carbon dioxide decreased significantly in all groups after air injections. The difference in concentration of oxygen in the inspiratory and expiratory gas (O_2 (I − E)) was lowest in the air group after both injections of air. On the basis of our studies we suggest that nitrous oxide should not be used during surgery associated with an increased risk of venous air embolism. (*Br. J. Anaesth.* 1996; **77:** 658–661)

Key words

Oxygen, inspired concentration. Ventilation, mechanical. Anaesthetics gases, nitrous oxide. Embolism, air. Pig.

The incidence of venous air embolism (VAE) has varied from 6% to more than 30% in patients undergoing surgery in the sitting position[1–3] and episodes of VAE have also been reported during orthopaedic operations.[4] Suggested alternatives for maintenance of anaesthesia during posterior fossa surgery include volatile anaesthetics in 100% oxygen, in nitrous oxide in oxygen or in air in oxygen.[5–7] Using nitrous oxide may facilitate detection of VAE,[8] but on the other hand, nitrous oxide may increase the size of the air bubbles and may therefore be detrimental. However, Losasso and co-workers[7] did not find any differences in the incidence of VAE in neurosurgical patients receiving 50% nitrous oxide in oxygen or 100% oxygen as part of isoflurane and fentanyl-based anaesthesia.

In a previous experimental study we demonstrated a decrease in airway compliance and an increase in pulmonary diastolic pressure after VAE during ventilation with 100% oxygen.[6] Simultaneous administration of nitrous oxide may further increase pulmonary vascular resistance in the case of VAE. Therefore, in this randomized, experimental study in pigs, we investigated the effects of three different mixtures of inspiratory gases, one of which included 50% nitrous oxide, on the detection and consequences of air embolism.

Materials and methods

The study was approved by the Animal Use and Care Committee of the hospital. We used 18 domestic pigs, weighing 17–22 kg, and the animals were unpremedicated. A vein on one ear was cannulated and Ringer's acetate was given i.v. Glycopyrronium 10 μg kg^{-1} was administered and anaesthesia was induced with a sleep dose of thiopentone. Pancuronium 0.2 mg kg^{-1} was used to facilitate tracheal intubation. Before instrumentation, fentanyl 5 μg kg^{-1} was given. Anaesthesia was maintained with isoflurane and nitrous oxide in 50% oxygen (six animals, nitrous oxide group), 100% oxygen (six animals, oxygen group) or 50% oxygen in nitrogen (six animals, air group). The concentration of isoflurane was adjusted to produce 0.7 MAC in a pig. The gas mixture used was selected randomly. Pancuronium, in 1-mg increments, was given as needed to maintain the animal paralysed throughout the experiment. The anaesthetic technique was similar to that used in patients undergoing surgery in the sitting position.

The ventilator used was a Servo 900C (Siemens Elema, Sweden). The inspiration–expiration flow ratio was set to 25% and the pause time to 10%. Ventilatory frequency was set to 20 bpm and tidal volume was adjusted to maintain $P\text{E}'_{CO_2}$ at 4.0–4.5%.

A side-stream spirometer (Datex Ultima, Instrumentarium, Finland) was connected to the ventilator tubing, providing continuous information on lung compliance, tidal volume and minute volume. The difference in concentration of oxygen in the inspiratory and expiratory gas (O_2 (I − E)), inspiratory and end-tidal isoflurane concentrations and $P\text{E}'_{CO_2}$ were analysed continuously and displayed on the same monitor screen.

One of the femoral arteries was cannulated for continuous monitoring of arterial pressure. A pulmonary artery catheter (size 5-French gauge) was

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introduced through the right jugular vein. Pulmonary artery pressures were monitored continuously. Haemoglobin saturation of oxygen (Sp_{O_2}) and ECG were monitored continuously.

Baseline values of arterial and pulmonary artery pressures, cardiac rhythm and rate, Sp_{O_2} and ventilatory variables were recorded. Air was then injected via the peripheral vein at a rate of 1 ml s^{-1}. Haemodynamic and ventilatory variables were recorded at the end of and 30 s after injection, and then at 1-min intervals for 10 min and every 2 min for another 10 min. The ratios of systolic arterial and pulmonary pressures were calculated after both injections of air to evaluate the magnitude of changes in pulmonary pressures at the time of ensuing circulatory collapse.

Each animal was tested with two injections of air. The volumes and order of injections were 1.0 ml kg^{-1} and 2.0 ml kg^{-1} and they were given 50 min apart. The doses used were based on our previous study.[6] After the experiment, the animals were killed with a toxic dose of barbiturate and i.v. injection of air 10 ml kg^{-1}.

Data were analysed using ANOVA. If significant differences were observed, the Fisher PLSD test was used for *post hoc* analysis. The results are presented as mean (SEM). $P < 0.05$ was considered statistically significant.

Results

All animals, except one, survived the air emboli; in one pig in the nitrous oxide group, 8 min after injection of 2.0 ml kg^{-1} of air, electromechanical dissociation was noted. No attempt was made at cardiopulmonary resuscitation and the results obtained after injection of 2.0 ml kg^{-1} of air in this animal were omitted from the analysis.

After injection of 1.0 ml kg^{-1} of air, systolic and diastolic arterial pressures decreased significantly in all groups and returned to baseline values within 5 min (table 1). After injection of 2.0 ml kg^{-1} of air, a significant decrease in systolic and diastolic pressures was observed in all groups at 30 s after the end of injection (table 2). At 16 min, systolic arterial pressure increased to a significantly higher level in the nitrous oxide group compared with the other groups (122 (6) mm Hg in the air group, 126 (7) mm Hg in the oxygen group and 156 (15) mm Hg in the nitrous oxide group; $P < 0.05$). The differences between the groups persisted to the end of the study period.

Pulmonary diastolic pressures increased after injection of air and the highest pressures were observed in the nitrous oxide group (fig. 1). The ratios of systolic pressures were highest in the nitrous oxide group after injection (fig. 2).

In the oxygen group, heart rate decreased from 140 (12) to 125 (13) beat min^{-1} at 30 s ($P < 0.05$) after injection of 1.0 ml kg^{-1} of air, and remained at this level until the end of the first study period. No significant changes were noted in the other groups. After injection of 2.0 ml kg^{-1} of air, changes in heart rate were not significant until 10 min, when heart rate had increased from 155 (7) to 194 beat min^{-1} in the nitrous oxide group ($P < 0.05$). At 8 min, heart rate was significantly higher in the nitrous oxide group than in the other groups (147 (15) beat min^{-1} in the air group, 136 (13) beat min^{-1} in the oxygen group and 194 (17) beat min^{-1} in the nitrous oxide group; $P < 0.05$). Heart rate remained significantly higher to the end of the study in the nitrous oxide group.

End-tidal concentration of carbon dioxide decreased significantly in all groups at 30 s after injection of 1.0 ml kg^{-1} of air and immediately after injection of 2.0 ml kg^{-1} of air (fig. 3).

There were no significant decreases in arterial saturation of oxygen after injection of 1.0 ml kg^{-1} of air. After injection of 2.0 ml kg^{-1} of air, Sp_{O_2} decreased from 100% to 77 (5) % in the nitrous oxide group ($P < 0.01$ between nitrous oxide and other groups). In the air group, the lowest observed Sp_{O_2} value was 88 (7) % at 5 min ($P < 0.05$ compared with

Table 1 Changes in systolic and diastolic arterial pressures after injection of 1.0 ml kg^{-1} of air (mean (SEM)). *$P<0.05$, **$P<0.01$, ***$P<0.001$ within groups, compared with baseline; †$P<0.05$ between the nitrous oxide (N_2O) and oxygen (O_2) groups; ‡$P<0.05$, between the N_2O and other groups

Time	Air group	O_2 group	N_2O group
Systolic arterial pressures (mm Hg)			
Baseline	120 (5)	125 (5)	136 (12)
After injection	115 (5)	118 (6)	121 (10)
30 s	105 (4)***	108 (5)***	97 (16)**
1 min	101 (4)***	105 (4)***	71 (18)***†
2 min	104 (5)***	102 (4)***	69 (16)***‡
3 min	107 (4)**	106 (5)***	82 (15)**
4 min	113 (3)	109 (4)***	99 (14)*
5 min	116 (4)	115 (4)*	120 (12)
6 min	118 (4)	119 (4)	134 (13)
Diastolic arterial pressures (mm Hg)			
Baseline	80 (6)	85 (6)	96 (8)
After injection	78 (5)	82 (6)	89 (11)
30 s	71 (5)*	74 (5)**	67 (11)*
1 min	69 (5)**	70 (5)***	48 (13)**
2 min	69 (6)**	69 (4)***	45 (12)***‡
3 min	72 (5)*	69 (5)***	52 (13)**
4 min	77 (5)	73 (4)***	63 (12)*
5 min	79 (5)	78 (4)	80 (10)
6 min	81 (6)	81 (4)	93 (10)

Table 2 Changes in systolic and diastolic arterial pressures after injection of 2.0 ml kg^{-1} of air (mean (SEM)). *$P<0.05$, **$P<0.01$, ***$P<0.001$ within groups, compared with baseline; †$P<0.05$ between the nitrous oxide (N_2O) and other groups; ‡$P<0.05$, between the air and N_2O group

Time	Air group	O_2 group	N_2O group
Systolic arterial pressures (mm Hg)			
Baseline	117 (7)	123 (7)	119 (9)
After injection	102 (6)	106 (7)	91 (10)
30 s	76 (12)***	71 (9)***	36 (3)***†
1 min	74 (13)***	65 (12)***	31 (3)***‡
2 min	75 (13)***	71 (14)***	44 (2)***
3 min	98 (15)*	72(20)***	61 (11)***
4 min	106 (12)	101 (15)*	71 (13)**
5 min	114 (8)	111 (12)	82 (18)*
6 min	123 (8)	122 (9)	90 (19)*
Diastolic arterial pressures (mm Hg)			
Baseline	78 (9)	83 (6)	81 (8)
After injection	66 (7)	73 (7)	57 (7)*‡
30 s	49 (9)**	43 (7)***	23 (3)***
1 min	48 (11)**	51 (12)*	21 (3)***
2 min	49 (13)**	45 (11)**	27 (2)***
3 min	65 (12)	56 (11)*	31 (5)***‡
4 min	72 (11)	65 (10)	36 (6)***†
5 min	76 (7)	72 (7)	41 (9)**†
6 min	80 (6)	80 (5)	49 (13)**†

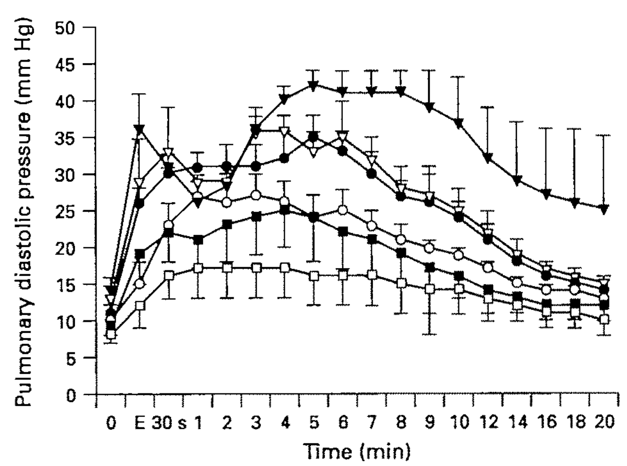

Figure 1 Changes in pulmonary diastolic pressure after injection of air: air group 1.0 ml kg^{-1} (●) and 2.0 ml kg^{-1} (○) of air, respectively; oxygen group, 1.0 ml kg^{-1} (■) and 2.0 ml kg^{-1} (□) of air, respectively; nitrous oxide group, 1.0 ml kg^{-1} (▼) and 2.0 ml kg^{-1} (▽) of air, respectively. 0 = Baseline, E = immediately after the end of injection of air. There were significant increases after injection of 1.0 ml kg^{-1} of air ($P < 0.001$) in the air group and nitrous oxide group immediately after the end of injection (E), and in the oxygen group at 30 s. Values returned to baseline at 18 min in the air group and at 14 min in the oxygen and nitrous oxide groups. There were significant differences ($P < 0.05$) between the oxygen and nitrous oxide groups from baseline to 18 min and significant increases after injection of 2.0 ml kg^{-1} of air in the air group ($P < 0.001$) from immediately after the end of the injection (E) to 12 min , in the oxygen group ($P < 0.001$) from E to 8 min, and in the nitrous oxide group ($P < 0.01$) at E, and again from 3 min to 12 min. There were significantly lower values in the oxygen group ($P < 0.05$ or $P < 0.01$) from baseline to 1 min, and from 4 min to 16 min.

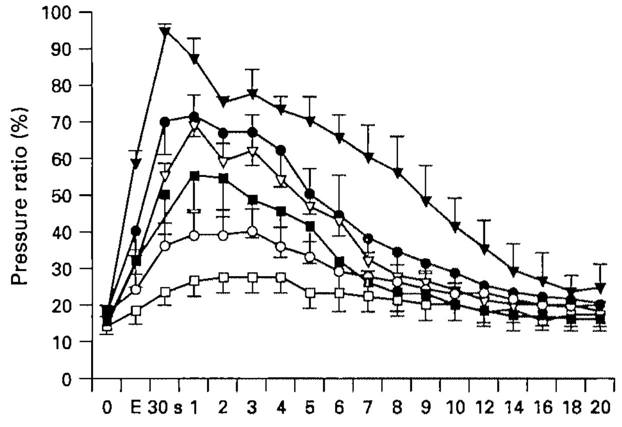

Figure 2 Changes in systolic pressure ratios after injection of air: air group 1.0 ml kg^{-1} (●) and 2.0 ml kg^{-1} (○) of air, respectively; oxygen group, 1.0 ml kg^{-1} (■) and 2.0 ml kg^{-1} (□) of air, respectively; nitrous oxide group, 1.0 ml kg^{-1} (▼) and 2.0 ml kg^{-1} (▽) of air, respectively. 0 = Baseline, E = immediately after the end of injection of air. There were significant increases after injection of 1.0 ml of air ($P < 0.05$) in the nitrous oxide group immediately after injection of air (E) and in all groups at 30 s ($P < 0.001$). Values returned to baseline at 9 min in the air group, 16 min in the oxygen group and 7 min in the nitrous oxide group. There were significant differences between the groups: $P < 0.05$ at E, 3 and 5 min, oxygen *vs* nitrous oxide group; $P < 0.001$ at 30 s, 1 and 2 min, and $P < 0.05$ at 4 min, nitrous oxide *vs* other groups. After injection of 2.0 ml kg^{-1} of air, there were significant increases at the end of injection: $P < 0.001$ in the air and nitrous oxide groups immediately after the end of injection (E), $P < 0.01$ in the oxygen group at E and $P < 0.001$ at 30 s. Values returned to baseline at 12 min in the air group, at 8 min in the oxygen group and at 16 min in the nitrous oxide group. There were significantly higher values in the nitrous oxide group: $P < 0.05$ from E to 3 min, at 5 min, and from 9 min to 12 min, $P < 0.01$ from 6 min to 8 min.

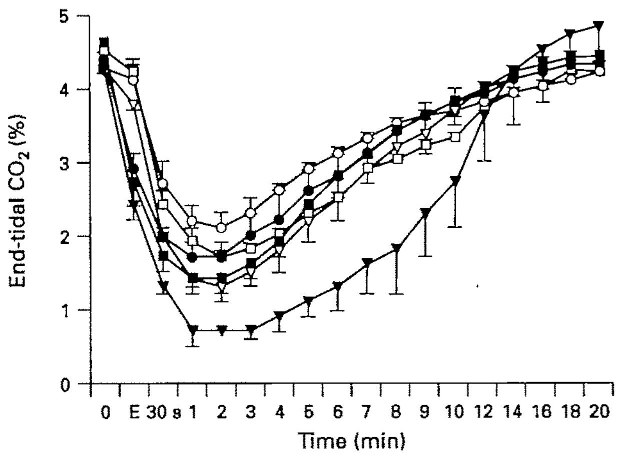

Figure 3 Changes in end-tidal concentration of carbon dioxide (CO_2) after injection of air: air group 1.0 ml kg^{-1} (●) and 2.0 ml kg^{-1} (○) of air, respectively; oxygen group, 1.0 ml kg^{-1} (■) and 2.0 ml kg^{-1} (□) of air, respectively; nitrous oxide group, 1.0 ml kg^{-1} (▼) and 2.0 ml kg^{-1} (▽) of air, respectively. 0 = Baseline, E = immediately after the end of injection of air. There were significant decreases after injection of 1.0 ml kg^{-1} of air ($P < 0.001$) from 30 s to 7 min in the air group, to 14 min in the oxygen group and to 9 min in the nitrous oxide group. Values returned to baseline at 12 min in the air and nitrous oxide groups. In the oxygen group, there were significant differences ($P < 0.05$) at 20 min compared with baseline. Differences between the groups: $P < 0.05$ between the air group and nitrous oxide group at 1, 2, 3, 6 and 8 min, and between the air group and other groups at 4 and 5 min. There were significant decreases after injection of 2.0 ml kg^{-1} of air: in the air group, $P < 0.05$ at 8 min, $P < 0.001$ from E to 7 min; in the oxygen group, $P < 0.05$ at 14 and 16 min, $P < 0.01$ at 12 min, $P < 0.001$ from E to 10 min; in the nitrous oxide group, $P < 0.05$ at 10 min, $P < 0.01$ from E and 9 min, $P < 0.001$ from 30 s to 8 min. Values were lowest in the nitrous oxide group: $P < 0.05$ at 30 s and at 9 min, $P < 0.01$ from 1 min to 8 min.

baseline) and in the oxygen group 80 (15) % at 1 min ($P < 0.05$ compared with baseline). In the nitrous oxide group the lowest recorded value was noted at 8 min, but on several occasions poor perfusion to the tail rendered monitoring of Sp_{O_2} impossible.

The difference in concentration of oxygen in the inspiratory and expiratory gas (O_2 (I − E)) was lowest in the air group after both injections of air (fig. 4).

Changes in airway compliance were similar in all groups. After injection of 1.0 ml kg^{-1} of air, compliance decreased from 21 (2) to 19 (2) ml cm H_2O^{-1} in the air group at 5 min ($P < 0.05$), from 20 (2) to 19 (2) ml cm H_2O^{-1} in the oxygen group at 30 s ($P < 0.01$) and from 20 (1) to 17 (1) ml cm H_2O^{-1} in the nitrous oxide group at 1 min ($P < 0.05$). After injection of 2.0 ml kg^{-1} of air significant changes occurred at 30 s, and were from 18 (2) to 16 (3) ml cm H_2O^{-1} ($P < 0.01$), from 17 (2) to 16 (2) ml cm H_2O^{-1} ($P < 0.05$) and from 16 (2) to 14 (1) ml cm H_2O^{-1} ($P < 0.05$) in the air, oxygen and nitrous oxide groups, respectively.

Discussion

The haemodynamic changes after VAE were slightly smaller than those noted in our previous study, in which three doses of air were injected into the right atrium at 50-min intervals.[6] In this study, air was injected via a peripheral vein in an attempt to better mimic an air embolism during craniotomy. Furthermore, we evaluated only the effects of two doses of

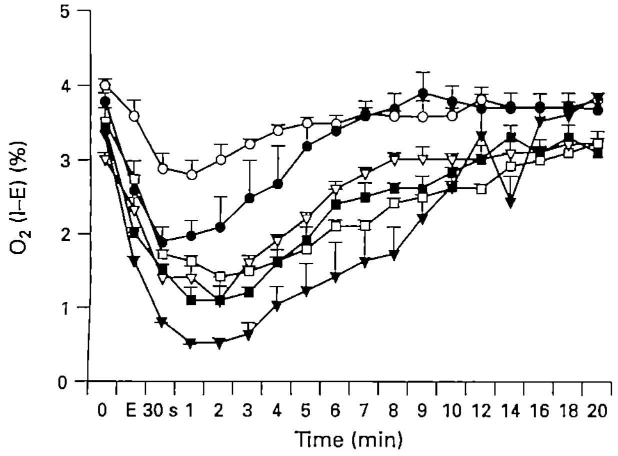

Figure 4 Changes in the difference in concentration of oxygen in the inspiratory and expiratory gas (O_2 (I – E)) after injection air: air group 1.0 ml kg^{-1} (●) and 2.0 ml kg^{-1} (○) of air, respectively; oxygen group, 1.0 ml kg^{-1} (■) and 2.0 ml kg^{-1} (□) of air, respectively; nitrous oxide group, 1.0 ml kg^{-1} (▼) and 2.0 ml kg^{-1} (▽) of air, respectively. 0 = Baseline, E = immediately after the end of injection of air. There were significant decreases after injection of 1.0 ml kg^{-1} of air: in the air group, $P < 0.05$ from 6 min to 10 min, $P < 0.01$ at 5 min, $P < 0.001$ from 30 s to 4 min; in the oxygen group, $P < 0.01$ at 14 and 16 min, $P < 0.001$ from E to 12 min; in the nitrous oxide group, $P < 0.05$ at 6 min, $P < 0.01$ at E, $P < 0.001$ from 30 s to 5 min. Differences between groups: air group *vs* other groups, $P < 0.01$ at 0 to 4 min, and from 14 min to 20 min, all other times significant differences ($P < 0.001$) between all groups. There were significant decreases after injection of 2.0 ml kg^{-1} of air in the air group: $P < 0.01$ at E, 3 and 4 min, $P < 0.001$ from 30 s to 2 min; in the oxygen group $P < 0.05$ at 16 min, $P < 0.01$ at 10 and 12 min, $P < 0.001$ from E to 9 min; in the nitrous oxide group, $P < 0.05$ at 9 min, $P < 0.001$ from E to 8 min. Differences between groups: $P < 0.05$ at 0 min between air group and nitrous oxide group. Significant differences between all groups from E to 10 min.

air, thus the cumulative effect of VAE was expected to be less evident. Our previous results suggested that some air can remain in the pulmonary circulation thus creating cumulative effects of two air emboli.[6]

It has been suggested that 50% nitrous oxide in the inspiratory gas mixture can be used safely provided it is discontinued after VAE has occurred.[7] We did not include discontinuation of nitrous oxide in our study design because in a clinical situation diagnosis of VAE can be delayed or missed. Furthermore, even if VAE is diagnosed promptly, nitrous oxide cannot be washed out immediately.

We observed marked increases in pulmonary pressures after VAE, consistent with previous results.[6] The changes were most prominent in animals receiving nitrous oxide. Similar changes have been observed after venous carbon dioxide embolism in experimental animals.[9] The increases in pulmonary pressures in this study not only reflected changes in pulmonary vascular resistance, but also mechanical block caused by air embolism. Cardiac output was not measured in this study because injection of air (which conducts heat poorly) would have affected the thermodilution technique.

The small haemodynamic changes after VAE in the oxygen group suggested that the use of 100% inspiratory oxygen is preferable to oxygen in air when there is increased risk of VAE during surgery.

A study be Vik and co-workers demonstrated that when VAE exceeds a certain threshold volume, breakthrough of air from pulmonary arteries to the systemic circulation occurs.[10] The volumes used in their study were comparable with those we injected. Even small bubbles of air may be detrimental in end arteries and nitrous oxide aggravates these effects by enlarging the size of the bubbles.

Changes in the inspiratory to expiratory end-tidal oxygen difference in healthy subjects are not dependent on cardiac output but on ventilation and metabolism.[11] In our earlier report, oxygen extraction diminished progressively with VAE.[6] In the present study, the changes were greater in the nitrous oxide and oxygen groups than in the air group. We used a constant minute ventilation and metabolism can be assumed to be similar in the animals. Thus we speculate that our observations are in part related to greater oxygen reserves in the oxygen group resulting in decreased uptake of oxygen when acute VAE caused diminished gas exchange. The difference between the nitrous oxide and air groups may be a manifestation of a greater decline in the gas exchange capacity in the former group, probably as a result of enlarged air bubbles.

In summary, on the basis of our studies we suggest that nitrous oxide should not be used during surgery associated with an increased risk of venous air embolism.

Acknowledgement

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References

1. Stanfeder M, Bay JW, Trusso R. The sitting position in neurosurgery: a retrospective analysis of 488 cases. *Neurosurgery* 1984; **14**: 649–658.
2. Matjasko J, Petrozza P, Cohen M, Steinberg P. Anesthesia and surgery in the seated position: analysis of 554 cases. *Neurosurgery* 1985; **17**: 695–702.
3. Dash HH, Bithal PK, Joshi S, Saini SS. Airway pressure monitoring as an aid in the diagnosis of air embolism. *Journal of Neurosurgical Anesthesiology* 1993 ; **5**: 159–163.
4. Spiess BD, Sloan MS, Matz SD, Lubenow TR, Ivankovich AD. Incidence of venous air embolism in total hip arthroplasty. *Anesthesia and Analgesia* 1986; **65**: S150.
5. Young ML. Posterior fossa: Anesthetic considerations. In: Cottrell JE, Smith DS, eds. *Anesthesia and Neurosurgery*. St Louis: Mosby, 1994; 339–363.
6. Kyttä J, Randell T, Tanskanen P, Kajimoto Y, Rosenberg PH. Monitoring lung compliance and end-tidal oxygen content for the detection of venous air embolism. *British Journal of Anaesthesia* 1995; **75**: 447–451.
7. Losasso TJ, Muzzi DA, Dietz NM, Cucchiara RF. Fifty percent nitrous oxide does not increase the risk of venous air embolism in neurosurgical patients operated upon in the sitting position. *Anesthesiology* 1992; **77**: 21–30.
8. Losasso TJ, Black S, Muzzi DA, Michenfelder JD, Cucchiara RF. Detection and consequences of venous air embolism. *Anesthesiology* 1992; **77**: 148–152.
9. Nyarwaya J-B, Pierre S, Mazoit J-X, Umbrain V, Romain M, Samii K, D' Hollander A. Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets. *British Journal of Anaesthesia* 1996; **76**: 428–434.
10. Vik A, Brubakk AO, Hennessy TR, Jenssen BM, Ekker M, Slørdahl SA. Venous air embolism in swine: transport of gas bubbles through the pulmonary circulation. *Journal of Applied Physiology* 1990; **69**: 237–244.
11. Bengtsson J, Ederberg S, Stenqvist O, Bengtson JP. Do changes in cardiac output affect the inspiratory to end-tidal oxygen difference? *Acta Anaesthesiologica Scandinavica* 1995; **39**: 1075–1079.

British Journal of Anaesthesia 1996; 77: 662–664

SHORT COMMUNICATION

Use of the fibrescope–video camera system for difficult tracheal intubation

K. AOYAMA, I. TAKENAKA, T. SATA AND A. SHIGEMATSU

Summary

We describe an alternative technique for difficult intubation using a fibrescope and a video camera system. The fibrescope attached to the video camera was passed nasally, which provided a view of the larynx on the monitor screen. Then the operator inserted a tracheal tube into the trachea orally using a second fibrescope or a stylet under video visual control. This technique permits a view of the tube passing through the vocal cords in patients who present difficulty in intubation. (*Br. J. Anaesth.* 1996; **77**: 662–664)

Key words

Intubation tracheal. Intubation tracheal, technique. Intubation tracheal, difficult. Equipment, fibrescope. Equipment, video camera.

Fibreoptic intubation is a reliable method for tracheal intubation in patients with difficult airways.[1 2] However, advancement of the tracheal tube over the fibrescope cannot be seen by conventional techniques. Despite intratracheal placement of the fibrescope, difficulty can be encountered while passing the tracheal tube through the vocal cords because the tube bevel is caught on the laryngeal structure.[1–3] Although rotating the tube while re-advancing may solve the problem, several attempts are sometimes required and damage to the larynx may occur.[2] In addition, the blindly advanced tracheal tube may enter the oesophagus, and its recognition is occasionally difficult.[2 4] We report an alternative intubation technique using a fibrescope attached to a video camera monitor system, which permits a view of passage of the tube into the glottis in patients who present with difficulty in intubation.

Methods and results

A 51-yr-old, 55-kg man was undergoing partial gastrectomy. His previous anaesthetic record revealed that the lungs had been ventilated easily by mask, while intubation with direct laryngoscopy was impossible. Fibrescope-guided oral intubation had been performed, but difficulty had been encountered while advancing the tube over the fibrescope. Even with the jaw thrust manoeuvre or with an aid of a rigid laryngoscope, multiple attempts at fibreoptic intubation had been required. During attempts, oesophageal intubation had occurred which was recognized by capnography. This history was explained to the patient, but he refused awake intubation. Thus we planned to insert a fibrescope attached to a video camera into the nasopharynx to observe advancement of the tracheal tube during oral fibreoptic intubation.

The patient was monitored by electrocardiography, indirect arterial pressure, pulse oximetry and capnography. After induction of general anaesthesia with thiopentone 250 mg, the patient's lungs were ventilated easily with 1–2% isoflurane in oxygen via a face mask. Neuromuscular block was produced with vecuronium 6 mg. After administration of a vasoconstrictor, a 6.5-mm i.d. Linder nasopharyngeal airway was inserted into the nostril and an Ovassapian intubating airway into the mouth. During mask ventilation, a 4.9-mm o.d. fibreoptic bronchoscope (FOB, Olympus, BF P-30) attached to a video camera monitor system (Olympus, OTV-F3) was passed through a face mask diaphragm into the nasopharyngeal airway by an assistant and a complete view of the glottis was displayed on the television screen (fig. 1).

After the mask was removed with the FOB left in place through the mask diaphragm, the operator inserted another fibreoptic laryngoscope (FOL, Olympus, LF-1), which was passed into the tracheal tube previously, through the airway intubator into the pharynx. The FOL was passed easily into the trachea, but the tracheal tube could not be advanced over the FOL. The tracheal tube caught on the right arytenoid cartilage was seen on the video monitor. The tracheal tube was then advanced with rotation and passed through the cords under video visual control. After passage of the tube through the glottis into the trachea was confirmed visually on the monitor screen, the FOB and FOL were removed. Successful intubation was confirmed further by capnography and clinical signs. Anaesthesia was

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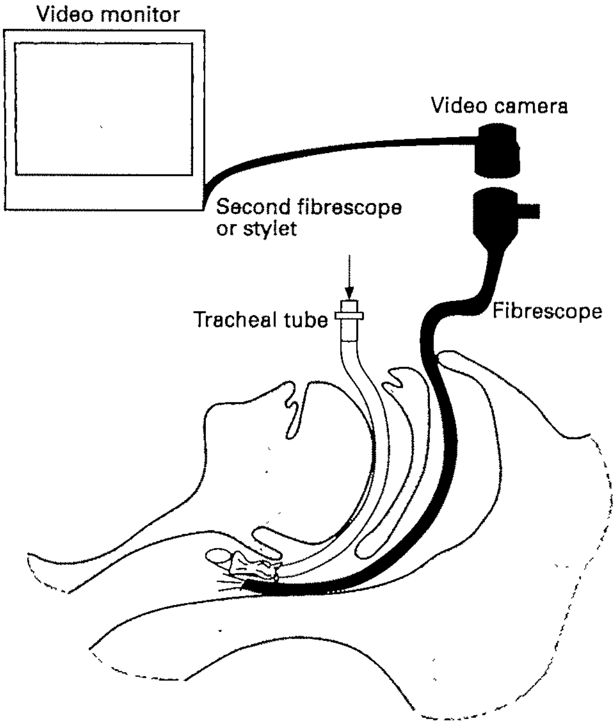

Figure 1 Intubation technique using a fibrescope and a video camera system. The fibrescope attached to the video camera is passed into the nasopharynx, which provides a view of the larynx on the video monitor. An operator can insert a tracheal tube into the trachea orally using a second fibrescope or a stylet under video visual control. This technique permits a view of passage of the tube into the glottis in patients who present with difficulty in intubation.

maintained with isoflurane and nitrous oxide in oxygen. Surgery and recovery were uneventful.

A 62-yr-old, 65-kg man was undergoing acromioplasty. Preanaesthetic examination revealed Mallampati class 2 and one-third reduction of atlanto–occipital joint extension. Anaesthesia was induced with fentanyl 100 μg and thiopentone 300 mg, and neuromuscular block was produced with vecuronium 7 mg. With conventional laryngoscopy, only the epiglottis could be seen despite application of external laryngeal pressure and manipulation of the head position. Several attempts using a straight blade, a longer Macintosh blade (No. 4) or a curved stylet were made by two experienced anaesthetists, but intubation failed. Then, the view of the larynx was obtained on a video monitor using an FOB and a video camera, as described in the first patient. The operator inserted a tracheal tube, equipped with a lubricated curved stylet, into the mouth with the jaw pulled forward and advanced the tracheal tube into the glottis under video visual control. Passage of the tube between the cords was confirmed visually. Successful placement of the tube was confirmed further by capnography.

Comment

This is the first report of tracheal intubation performed under video visual control in patients presenting with difficulty in intubation. The fibrescope, attached to the video camera and passed nasally, provided an excellent view of the larynx on the monitor screen, even in patients who presented with difficulty in intubation, during and after intubation. When fibreoptic-guided oral intubation was performed using a second fibrescope, this technique allowed a view of advancement of the tracheal tube over the second fibrescope. When difficulty was encountered while passing the tracheal tube through the cords, we rotated the tube and re-advanced it under video visual control. We did not re-advance the tube blindly, as a blind manoeuvre, even with the aid of a rigid laryngoscope, had been difficult previously. In our experience, direct vision of the tube rotation and tube advancement could help to introduce the tracheal tube into the glottis smoothly and so avoid tissue damage. In addition, our technique permits a view of the tube passing through the vocal cords, which could be useful in confirming correct placement of the tracheal tube. Intratracheal placement of the tube should be confirmed further by capnography, oximetry and traditional clinical signs after this technique. Another advantage of our technique is that both the operator and assistants can view the airway, and therefore help each other.

We could easily perform oral tracheal intubation using a stylet instead of the second fibrescope, as described in the second patient. This technique requires only one fibrescope. The tracheal tube with the curved stylet as a hockey stick could be placed around the tongue without the use of a laryngoscope and introduced into the trachea under video visual control. This technique can be used in combination with a bougie.

The concept of our technique seems to be similar to that of some rigid fibreoptic laryngoscopes, including the Bullard laryngoscope, the Upsherscope and the Wu scope system, which permit a view of passage of the tube through the glottis on a video monitor. Although these devices may be available in patients with difficult intubation, there are some cases in which the rigid blade or fixed intubating mechanism, or both, was unsuitable.[5] Our technique may be an acceptable alternative in these patients because a flexible fibrescope can be manipulated freely to view the glottis and the tracheal tube can be controlled independently with a second fibrescope or a stylet.

A disadvantage of our technique is the necessity to use the nasal route, some equipment and an assistant. Our technique may be unsuitable in patients with coagulopathy, intranasal pathology and basilar skull fracture. Although there is the potential for nasal bleeding, we used the vasoconstrictor and the Linder nasopharyngeal airway to avoid this. This airway can be inserted with a soft inflatable introducer, which can minimize tissue damage.[6]

We suggest that the use of the fibrescope–video camera system may be available for management of difficult intubation. This technique may be useful where conventional fibreoptic techniques are difficult or fail. Then, if only one fibrescope is available, the technique used in the second case can be used. However, further studies are needed to determine the usefulness of this technique.

References

1. Cobley M, Vaughan RS. Recognition and management of difficult airway problems. *British Journal of Anaesthesia* 1992; **68**: 90–97.
2. Ovassapian A, Wheeler M. Fiberoptic endoscopy-aided techniques. In: Benumof JL, eds. *Airway Management: Principles and Practice*. St Louis: Mosby, 1995; 282–319.
3. Katsnelson T, Frost EAM, Farcon E, Goldiner PL. When the endotracheal tube will not pass over the flexible fiberoptic bronchoscope. *Anesthesiology* 1992; **76**: 151–152.
4. Moorthy SS, Dierdorf SF. An unusual difficulty in fiberoptic intubation. *Anesthesiology* 1985; **63**: 229.
5. Cooper SD. The evolution of upper-airway retraction: New and old laryngoscopy blades. In: Benumof JL, eds. *Airway Management: Principles and Practice*. St Louis: Mosby, 1995; 374–411.
6. Gallagher WJ, Pearce AC, Power SJ. Assessment of a new nasopharyngeal airway. *British Journal of Anaesthesia* 1988; **60**: 112–115.

British Journal of Anaesthesia 1996; 77: 665–668

CASE REPORTS

General anaesthesia for Caesarean section in a parturient with Noonan's syndrome

H. A. McLure and S. M. Yentis

Summary

We describe the anaesthetic management of a parturient with Noonan's syndrome. Her problems included severe cardiac disease, facial abnormalities and extreme phobia to needles. After intrauterine death at 30 weeks' gestation, induction of labour was attempted and extradural analgesia initiated using low-dose bupivacaine. She failed to progress and underwent Caesarean section under general anaesthesia using awake oral fibreoptic intubation. (*Br. J. Anaesth.* 1996; **77**: 665–668)

Key words
Complications, Noonan's syndrome. Complications, cardiomyopathy. Anaesthesia, obstetric.

Noonan's syndrome is a clinical entity resembling Turner's syndrome but with a normal karyotype.[1] Features include facial, skeletal and cardiovascular abnormalities. There has been only one case report of anaesthesia for Caesarean section in a parturient with Noonan's syndrome, using regional anaesthesia.[2] We describe the management of a parturient with Noonan's syndrome who required analgesia for labour, then general anaesthesia for Caesarean section.

Case report

A 25-yr-old primigravida with Noonan's syndrome was referred to the obstetric anaesthetic high-risk clinic at 14 weeks' gestation. She was known to have cardiomyopathy, and was under regular cardiological review having undergone pulmonary, aortic and mitral valvotomy with excision of left and right ventricular outflow obstruction at the age of 12 yr. Her maintenance therapy included iron supplementation, digoxin 250 μg, amiloride 5 mg and frusemide 40 mg once daily, and sotalol 40 mg twice daily. Haematological investigation revealed no coagulation or platelet defects. She had atrial fibrillation (AF) with a dilated left atrium and so was at risk of embolic events. She therefore received the low molecular weight heparin (LMWH) enoxaparin 40 mg s.c. once daily, which was changed to warfarin at 12 weeks' gestation after small vaginal bleeds. She was dyspnoeic on climbing one flight of stairs and had occasional palpitations associated with dyspnoea and chest tightness. On examination she had AF with a ventricular frequency of 110–130 bpm, arterial pressure (AP) of 110/50 mm Hg, with no evidence of cardiac failure. Chest x-ray showed evidence of previous surgery. An electrocardiogram (ECG) revealed AF, left axis deviation with left bundle branch block and septal hypertrophy. Echocardiographic findings included a dilated left atrium (5.5 cm) with mitral stenosis (estimated area 2.5 cm^2, peak gradient 23 mm Hg, mean 10 mm Hg), a hypoplastic pulmonary valve and mild regurgitation in all valves. Overall left ventricular function was impaired with a fractional shortening of 30%. The interventricular septum was thickened (1.2 cm) with no evidence of outflow tract obstruction.

Her face was typical of Noonan's syndrome with hypertelorism, downward slanting palpebral fissures and thickened hooded eyelids. She had a depressed nasal root with a wide base, small jaw, normal gape (Mallampati grade II) and a "nasal" voice. She had the characteristic "shield" chest deformity of pectus carinatum superiorly and pectus excavatum inferiorly, but minimal neck webbing. Her intelligence appeared normal, although she had a morbid fear of needles.

At 23 weeks' gestation the cardiologists stopped administration of sotalol because of concerns about its negative inotropic effects. One week later she was admitted to another hospital with pulmonary oedema and tachycardia of 150–160 beat min^{-1}. An echocardiograph showed worsened left ventricular function. She was started on propranolol 10 mg three times daily with clinical and echocardiographic improvement. After antepartum haemorrhage at 27 weeks' gestation she was admitted to our hospital. Her international normalized ratio (INR) was 3.8. Warfarin therapy was stopped and replaced with the LMWH dalteparin 5000 u. s.c. once daily. Repeat echocardiography studies were unchanged. Serial cardiotocographs (CTG) were unremarkable, and a scan at 28 weeks' showed normal fetal growth. Plans were made with the anaesthetic department for elective Caesarean section at 38 weeks. At 30 weeks the baby was noted to be less active with reduced fetal heart rate variability on CTG. On the following

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morning no fetal movements were felt. CTG failed to find a heart beat and ultrasound examination confirmed *in utero* death.

The obstetric team chose to induce labour that afternoon. After discussing the analgesic options with the patient, an extradural technique was chosen. Physical examination showed a 65-kg pregnant woman, height 157 cm, with AF: ventricular frequency 105–115 bpm, AP 100/65 mm Hg, without evidence of cardiac failure. Investigations revealed a haemoglobin concentration of 11.6 g dl^{-1}, platelets 187 × 10^9 $litre^{-1}$, prothrombin time 15 s, activated partial thromboplastin time 32 s, thrombin time 10 s, sodium 137 mmol $litre^{-1}$, potassium 3.8 mmol $litre^{-1}$, urea 2.4 mmol $litre^{-1}$ and creatinine 49 μmol $litre^{-1}$. Her last dose of LMWH had been given 20 h previously. Non-invasive AP, ECG and pulse oximetry were applied, and oxygen administered via nasal cannulae. She was extremely anxious about needles and so required EMLA for siting an i.v. cannula, then slow increments of midazolam i.v. to a total of 5 mg for insertion of the extradural catheter. Systolic AP decreased to 80 mm Hg but returned to 100 mm Hg with 250 ml of crystalloid. An extradural was sited at L2–3 in the left lateral position. Over the next 30 min she received four 5-ml extradural boluses of 0.1% bupivacaine, achieving a decrease in cold sensation to T9, but no motor block or haemodynamic instability. Dinoprostone 1 mg was then administered vaginally to induce labour, and she was started on regular oral ranitidine.

The following morning the cervix remained unfavourable. As induction of labour had proved unsuccessful the decision was made to proceed to Caesarean section. She had received no further extradural bupivacaine and no sensory block was detectable. Again anaesthetic options were discussed with the patient. She adamantly refused any invasive tests or monitoring while awake, and wished to be asleep during the operation. In view of her cardiac status, possible difficult airway and risk of acid aspiration, general anaesthesia with an awake oral fibreoptic intubation was suggested as the safest option. She agreed only after lengthy discussions with her husband.

Antisialogue premedication of glycopyrronium 200 μg was given slowly i.v. with ECG monitoring. Heart rate remained at 100–112 beat min^{-1}. She was positioned semi-recumbent with a wedge under the right hip, received 30 ml of sodium citrate 0.3 mol $litre^{-1}$ orally, ampicillin 1 g and gentamicin 80 mg i.v., and was then sedated with increments of diazepam i.v. to a total dose of 10 mg. After two 10-mg sprays of lignocaine to the oropharynx, a flexible fibreoptic bronchoscope preloaded with a size 7 armoured tracheal tube was introduced via an Ovassapian oral airway. Topical anaesthesia was achieved using a "spray-as-you-go" technique with 4 ml of 4% lignocaine. This enabled the bronchoscope to be passed easily through the cords. The tracheal tube was "railroaded" into the trachea and its position confirmed by visual inspection of the carina. General anaesthesia was induced with fentanyl 700 μg and etomidate 4 mg i.v. followed by vecuronium 6 mg i.v. and the lungs ventilated with 50% nitrous oxide in oxygen to an end-tidal carbon dioxide concentration of 4.5-5%. When anaesthetized a left radial arterial catheter, right internal jugular central venous catheter and urinary catheter were sited. She remained haemodynamically stable allowing the slow introduction of 0.5% isoflurane. Direct laryngoscopy with the tube *in situ* gave a good view of the vocal cords. After delivery of a dead male fetus, Syntocinon 10 u. was administered over 10 min. A retroplacental blood clot suggesting placental abruption as the cause of death was noted. Heart rate was 105–130 beat min^{-1}, AP 105–115/60 mm Hg, central venous pressure 22–26 mm Hg and oxygen saturation at least 99% throughout intubation and surgery. Blood loss was minimal and peroperative transfusion amounted to 1.25 litre of crystalloid. At the completion of surgery the patient was transferred to the intensive care unit for postoperative care. Tracheal extubation occurred the following morning after an uneventful night. She left hospital after an uncomplicated recovery of 7 days, and is planning a further pregnancy.

Discussion

In 1963 Dr Jacqueline Noonan, a paediatric cardiologist, described a series of nine cases with congenital heart disease associated with a phenotype similar to Turner's syndrome, but with apparently normal chromosomes.[3] The main features included pulmonary stenosis, short stature, a webbed neck and typical facial abnormalities.[4] The characteristics distinguishing it from Turner's syndrome include karyotype analysis, sex distribution, fertility, the site of the cardiac lesion, facial appearance and the presence of mental retardation.[2]

Turner's syndrome occurs exclusively in females; Noonan's, although more common in males, is found in both sexes. Males often have cryptorchidism and are rarely fertile, whereas females have normal fertility but a delayed menarche.[2] The estimated incidence is 1 in 1000 to 1 in 2000 live births. The exact incidence is unknown.[1] It follows an autosomal dominant pattern with variable penetrance and expression.[5] Maternal transmission of the gene is said to be three times more common than paternal transmission.[6] With an affected parent there is a 50% risk of subsequent children inheriting the still unknown gene.[6]

Cardiac lesions are characteristically right-sided in Noonan's syndrome, compared with left-sided in Turner's syndrome.[7–9] The most frequently reported abnormality in Noonan's syndrome is pulmonary stenosis, usually with a dysplastic pulmonary valve. The annulus is normal in size but the cusps are thickened and immobile.[1] In one series, pulmonary stenosis occurred in 62%;[1] there was an atrial septal defect in 13% and septal hypertrophy in 6%. Hypertrophic cardiomyopathy was present in 20%. Only 12.5% of patients had a normal echocardiograph.[1] Other documented cardiac lesions include patent ductus arteriosus, aortic stenosis or coarctation, polyvalvular dysplasia, ventricular septal defects, systemic venous abnormalities and Fallot's tetralogy.[8]

The facial abnormalities of Noonan's syndrome include hypertelorism with downward slanting palpebral fissures, high arched eyebrows and thickened hooded eyelids, sometimes with a ptosis.[1] There may be low set ears with a thickened helix, and coarse curly hair with a low hair line at the back. The typical flattened mid face with depressed nasal root, wide nasal base, full upper lip, high arched palate, micrognathia and dental malocclusion combined with a webbed sometimes fused neck may present a challenge to the anaesthetist, making conventional oral or nasal intubation difficult, if not impossible.[2 9 10] These facial abnormalities usually become less marked with age, and are not a feature of Turner's syndrome.[1]

Musculoskeletal abnormalities include short stature, webbed neck and cubitus valgus.[8] The chest deformity is typical and gives the appearance of widely spaced nipples.[10] It may be associated with kyphoscoliosis and respiratory compromise.[10] Other features include joint contractures, cervical spine fusion and lumbar lordosis.[1] Association of Noonan's syndrome with malignant hyperpyrexia has not been substantiated.[1]

Abnormal bleeding and bruising are often seen in Noonan's syndrome (56–74%), associated with a mixed collection of defects in the platelet and coagulation systems.[6 11 12] Isolated factor XI deficiency has been recognized as the commonest single factor deficiency, and may be treated with single factor replacement.[6] Most of the bleeding problems are mild, and may only be revealed by surgery such as dental extraction. Interestingly, cases of severe postoperative bleeding have been reported despite normal *in vitro* clotting assays and platelet counts.[6]

Other associated features with anaesthetic implications include renal dysfunction, dermatological, hearing and visual abnormalities, and hepatosplenomegaly.[1 2 5]

Our patient was known to have impaired left ventricular function with multiple valvular involvement. Her cardiac status represented a significant risk not only for any anaesthetic intervention, but also for labour. Sympathetic stimulation of a painful labour exacerbated by episodic prolonged Valsalva manoeuvres, increases in blood volume with uterine contractions or reductions with bleeding could cause significant haemodynamic instability.[13–15] To avoid precipitating ventricular failure an analgesic technique was required which would reduce sympathetic stimulation and minimize variations in heart rate, contractility and filling pressures. A cautious extradural technique using low concentrations of local anaesthetic was therefore chosen. Higher concentrations of local anaesthetic are associated with greater disturbance in cardiovascular indices.[16] Extradural opioids were not administered although we intended to use these drugs if she went into labour.

Skeletal abnormalities in Noonan's syndrome may lead to difficulties with regional anaesthetic techniques.[2] Kyphoscoliosis and lumbar lordosis may make it difficult to position the patient for axial block. The bony vertebral spinal canal may be narrowed with a normal calibre spinal cord, thereby reducing the size of the extradural space. Location of the space may be more complicated with increased problems threading the catheter and less predictable spread of local anaesthetic.[2] Additional concerns in this patient focused on her potential coagulopathy with the possibility of an extradural haematoma. She had been treated with LMWH for embolic prophylaxis although she had not had a dose for 20 h. As her coagulation screen was normal it was thought that the benefits of extradural analgesia outweighed the risk of producing an extradural haematoma. Continuous subarachnoid analgesia would have been an alternative method. Theoretically, this might carry less risk of bleeding but exposes the patient to an increased risk of post-dural puncture headache.

Many of the typical facial features of Noonan's syndrome suggest a difficult airway, and additionally our patient was pregnant with an increased risk of acid aspiration. Although she had an extradural catheter already *in situ* the block had worn off many hours previously, and it was felt that her cardiac status represented a contraindication to the dense block that would be required for surgery, especially given her refusal of invasive monitoring.[16] For safe general anaesthesia tracheal intubation would be required. A fibreoptic technique was chosen using the oral route because of concerns about her abnormal nasal anatomy. Laryngoscopy after intubation was easy, providing a view of the whole glottis. This may influence subsequent anaesthetic management, although full assessment would be required at that time. A relatively high-dose opioid–nitrous oxide–oxygen technique was used initially as opioids have a relatively benign effect on myocardial contractility avoiding drug-induced myocardial depression.

In summary, patients with Noonan's syndrome present a multiplicity of challenges to the anaesthetist, particularly with regard to cardiovascular and airway abnormalities. Their fertility and improving results from cardiac surgery in children imply an increasing number may present to anaesthetic departments requesting analgesia and anaesthesia in the peripartum period. To achieve a successful outcome for mother and baby, Noonan's parturients must be detected early in pregnancy so that time is available to order appropriate investigations and formulate a suitable plan of action between obstetricians, midwives and anaesthetists.

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References

1. Sharland M, Burch M, McKenna WM, Patton MA. A clinical study of Noonan's syndrome. *Archives of Disease in Childhood* 1992; **67**: 178–183.
2. Dadabhoy ZP, Winnie AP. Regional anesthesia for Cesarean section in a parturient with Noonan's syndrome. *Anesthesiology* 1988; **68**: 636–638.
3. Noonan JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. *Journal of Pediatrics* 1963; **63**: 468–470.

4. Noonan JA. Hypertelorism with Turner phenotype. *American Journal of Diseases of Children* 1968; **116**: 373–380.
5. Collins E, Turner G. The Noonan syndrome—a review of the clinical and genetic features of 27 cases. *Journal of Pediatrics* 1973; **83**: 941–950.
6. Sugar AW, Ezsias A, Bloom AL, Morcos WE. Orthognathic surgery in a patient with Noonan's syndrome. *Journal of Oral and Maxillofacial Surgery* 1994; **52**: 421–425.
7. Van Der Hauwert LG, Fryus JP, Dumoulin M, Logghe N. Cardiovascular malformations in Turner's and Noonan's syndrome. *British Heart Journal* 1978; **40**: 500–509.
8. Pearl W. Cardiovascular anomalies in Noonan's syndrome. *Chest* 1977; **71**: 677–679.
9. Campbell AM, Bousfield JD. Anaesthesia in a patient with Noonan's syndrome and cardiomyopathy. *Anaesthesia* 1992; **47**: 131–133.
10. Schwartz N, Eisenkraft JB. Anaesthetic management of a child with Noonan's syndrome and idiopathic hypertrophic subaortic stenosis. *Anesthesia and Analgesia* 1992; **74**: 464–466.
11. Sharland M, Patton MA, Talbot S, Chitolie A, Bevan DH. Coagulation-factor deficiencies and abnormal bleeding in Noonan's syndrome. *Lancet* 1992; **339**: 19–21.
12. Emmerich J, Aiach M, Capron L, Fiessinger JN. Noonan's syndrome and coagulation-factor deficiencies. *Lancet* 1992; **339**: 431.
13. Oakley DG, McGarry K, Limb DG, Oakley CM. Management of pregnancy in patients with hypertrophic cardiomyopathy. *British Medical Journal* 1979; **1**: 1749–1750.
14. Tessler MJ, Hudson R. Pulmonary oedema in two parturients with hypertrophic obstructive cardiomyopathy. *Canadian Journal of Anaesthesia* 1990; **37**: 467–473.
15. Gambling DR, Flanagan ML, Huckell VF, Lucas SB, Kim JHK. Anaesthetic management and non-invasive monitoring for Caesarean section in a patient with cardiomyopathy. *Canadian Journal of Anaesthesia* 1987; **34**: 505–508.
16. Thompson RC, Liberthson RR, Lowenstein E. Perioperative anesthetic risk of non-cardiac surgery in hypertrophic obstructive cardiomyopathy. *Journal of the American Medical Association* 1985; **254**: 2419–2421.

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Use of rocuronium in a pregnant patient with an open eye injury, receiving magnesium medication, for preterm labour

R. R. GAISER AND E. H. SEEM

Summary

We present a case where rocuronium 80 mg (3 × ED_{95}) was used in a rapid sequence induction in a 80-kg pregnant patient with an open eye injury. The patient was also receiving magnesium 2 g h^{-1} i.v. for preterm labour. The expected duration for neuromuscular block of rocuronium in the absence of magnesium would be approximately 53 min; with infusion of magnesium, the duration of neuromuscular block was prolonged four-fold (215 min). It is important to remember that magnesium potentiates the effects of all non-depolarizing neuromuscular blocking agents, including rocuronium. (*Br. J. Anaesth.* 1996; **77**: 669–671)

Key words

Neuromuscular block, rocuronium. Ions, magnesium. Complications, eye injury.

Magnesium is used frequently in the USA both for pre-eclampsia as an anticonvulsant and for preterm labour. For the treatment of preterm labour, magnesium inhibits myometrial activity, but the mechanism of its tocolytic effect is unknown[1]; presumably myometrial contractility is depressed by modulating calcium uptake, binding or distribution in smooth muscle cells.[2] Serum concentrations of 4–8 mmol $litre^{-1}$ are required. Maternal side effects include nausea, vomiting, ileus, visual blurring, diplopia, headaches and the potential for pulmonary oedema.[3] Magnesium also causes increased sensitivity to neuromuscular blocking agents.[4] We present the first report of magnesium prolonging the neuromuscular blocking effect of rocuronium. Rocuronium was chosen as this patient also had an open eye injury with the concern that suxamethonium increases intraocular pressure.

Case report

The patient was a 31-yr-old parturient with a 28-week gestation and an unremarkable prenatal course who presented for repair of a penetrating eye injury. The patient was involved in a motor vehicle accident in which she was an unrestrained passenger. She suffered temporary loss of consciousness, but presented to the emergency room with a Glasgow coma scale of 15. Her injuries included laceration to the left forehead, corneal scleral laceration and prolapsed vitreal tissue of the left eye, and a left styloid fracture. Initial vital signs on presentation were: arterial pressure 140/88 mm Hg, heart rate 95 beat min^{-1}, temperature 36.5 °C and ventilatory frequency 18 bpm. Her height was 162 cm, weight 80 kg. She was placed in a cervical collar.

A CT scan of the head and neck revealed a ruptured left globe with medial wall fracture. The view of the cervical spine was unable to exclude injury. Other laboratory values included haemoglobin concentration 12.3 g dl^{-1}, packed cell volume 36.1%, blood urea nitrogen concentration 7 mg dl^{-1}, creatinine concentration 0.6 mg dl^{-1}, prothrombin time 12.2 s, activated partial thromboplastin time 28.3 s and fibrinogen concentration 358 mg dl^{-1}. Tocodynometry and continuous Doppler fetal heart tones were commenced to monitor uterine contractile activity and fetal heart rate, respectively. Fetal heart rate was 130–140 beat min^{-1} with good long- and short-term variability. Uterine contractions were occurring every 3 min, for which she received a loading dose of magnesium 4 g, and a continuous infusion of 2 g h^{-1} was started.

She was transferred to our hospital for operative management. Additional laboratory studies before induction of anaesthesia included a magnesium concentration of 5.8 mmol $litre^{-1}$ (therapeutic range 4–8 mmol $litre^{-1}$). In the operating room, a 16-gauge i.v. catheter was inserted into her right forearm. ECG, end-tidal carbon dioxide, pulse oximetry, fetal heart rate and uterine contraction monitoring with a tocodynometer, and neuromuscular block monitoring using a Neurotechnology peripheral nerve stimulator were commenced.

The patient was premedicated with sodium bicitrate 30 ml orally and metoclopramide 10 mg i.v. After placement in left uterine displacement and 5 min of preoxygenation with 100% oxygen, anaesthesia was induced with fentanyl 200 μg, thiopentone 400 mg and rocuronium 80 mg (0.9 mg kg^{-1}, 3 × ED_{95}). At 60 s, her train of four had disappeared and her trachea was intubated under direct laryngoscopy with a 7.0 tracheal tube. The patient did not cough during intubation and arterial pressure did not

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increase. Her oxygen saturation decreased to 90% but returned to 100% after intubation. Anaesthesia was maintained with isoflurane in oxygen and fentanyl.

Five minutes after induction, there was a decrease in short-term variability on the fetal heart rate monitor, with a heart rate of 140–150 beat min^{-1}. We could not detect post-tetanic facilitation until 110 min after induction and the first twitch in the train of four was detected 215 min after administration of rocuronium. When surgery was completed 6 h after induction, the patient had received a total of rocuronium 80 mg, fentanyl 450 µg and normal saline 1300 ml. The patient was transferred to the labour suite and was weaned from the magnesium infusion over the next 24-h period. The patient was discharged 6 days later with some return of vision in the left eye and no apparent adverse effects on the fetus.

Discussion

This case highlights an anaesthetic challenge of securing the airway in a pregnant patient with an open eye injury. In a pregnant trauma patient with a 28-week gestation, aspiration is a high risk. Pain from injury delays gastric emptying. The enlarging uterus during pregnancy displaces the stomach, altering the competence of the gastro-oesophageal sphincter.[5] Hormonal changes delay gastric emptying,[6] while gastrin excreted by the placenta increases the acidity of the maternal stomach contents.[7] The usual means of securing the airway in such a patient would be an awake intubation or rapid sequence induction using an induction agent, suxamethonium and cricoid pressure. However, our patient also had an open eye injury. Securing the airway by awake intubation is associated with an increase in intraocular pressure via venous congestion of the orbital veins associated with straining or coughing.[8] Suxamethonium also has been shown to increase intraocular pressure[9] with one case report of extrusion of vitreous from this increase.[10] Although pretreatment with a non-depolarizing neuromuscular blocker such as 3 mg of curare or vecuronium 1 mg has been advocated, this does not reliably prevent the increase.[11] The risk of extrusion of intraocular contents in a patient with an open eye injury given suxamethonium is rare; however, we chose to perform a rapid sequence induction using rocuronium as the neuromuscular blocking agent.

Rocuronium is a new steroidal neuromuscular blocking drug related chemically to vecuronium. However, unlike vecuronium, it is less potent with a shorter time to onset.[12] Given this shorter onset period, its use for rapid sequence induction has been investigated. Huizinga and colleagues demonstrated comparable intubating conditions with suxamethonium 1.5 mg kg^{-1}, at 60 and 90 s after administration of rocuronium 0.6 mg kg^{-1} (2 × ED_{95}).[13] Tryba and colleagues found that similar intubating conditions could be obtained with rocuronium 0.6 mg kg^{-1} or suxamethonium 1.5 mg kg^{-1}, provided the dose was administered immediately before administration of thiopentone; the conditions were less optimal if administered immediately after thiopentone.[14] Finally, Abouleish and colleagues investigated its use during Caesarean delivery. With a dose of 0.6 mg kg^{-1}, intubating conditions were poor with a thiopentone dose of 4 mg kg^{-1}; however, increasing the dose of thiopentone to 6 mg kg^{-1} improved intubating conditions.[15] If rapid securing of the airway in a patient with a contraindication to suxamethonium is necessary, rocuronium seems to be a good choice for neuromuscular block.

Rocuronium has been shown not to increase intraocular pressure.[16] Abouleish demonstrated no adverse effects on the neonate and pregnancy did not enhance its neuromuscular blocking properties. Given the gestational age of the fetus (second trimester), teratogenicity was not a concern. The dose chosen for our patient (0.9 mg kg^{-1}) was higher than the doses used in the above studies. By increasing the dose from 0.6 to 0.9 mg kg^{-1} (2 × ED_{95} to 3 × ED_{95}), the onset time decreased from 271 ± 129 s to 135 ± 79 s with excellent intubating conditions at 60 s. The duration to recovery of 25% of twitch increased from 27.3 ± 8.2 min to 53.0 ± 15.2 min.[17] We felt that rapid securing of the airway was important in this patient, as became evident from the decrease in oxygen saturation pulse oximetry reading, and we were willing to tolerate the prolonged duration. Although administration of a priming dose has been shown to reduce onset time,[18] we were concerned as the patient was receiving magnesium which increases sensitivity to non-depolarizing neuromuscular blocking agents.[19] A priming dose may have been sufficient to result in profound weakness in an awake patient.

Our patient was receiving concurrent magnesium therapy for preterm labour. Although the mechanism is unclear, magnesium has become the traditional agent used for the treatment of preterm labour. Side effects of magnesium include pulmonary oedema, sedation and potentiation of neuromuscular block. Therapeutic plasma concentrations are 4–8 mmol litre^{-1}. Our patient's magnesium concentration at the time of induction was 5.8 mmol litre^{-1}. The mechanism of its blocking effects at the neuromuscular junction is suppression of acetylcholine release at the neuromuscular junction or decrease in the depolarizing action of acetylcholine at the motor end-plate.[20] The time to achieve post-tetanic facilitation in this patient was 110 min and the time to achieve one twitch of a train of four was 215 min. Assuming that at 25% recovery of a twitch is when the first twitch of a train of four is perceptible, the duration was more than six times greater, supporting the contention that magnesium also prolongs the duration of action of rocuronium. Although isoflurane has also been shown to prolong the duration of rocuronium,[21] this effect cannot account for the dramatic increase in this our patient.

We were surprised by the obstetrician's concern for the loss of short-term variability on the fetal tracing after induction. This phenomenon has been described previously[22] and is attributed to the baby becoming anaesthetized. We do not feel that this can be attributed to rocuronium.

References

1. Spisso KR, Harbert GM, Thiagarabjah S. The use of magnesium sulfate as the primary tocolytic agent to prevent premature delivery. *American Journal of Obstetrics and Gynecology* 1982; **142**: 840–845.
2. Altura BM, Altura BT. Magnesium ions and contraction of vascular smooth muscles: Relationship to some vascular diseases. *Federal Proceedings* 1981; **40**: 2672–2679.
3. Wilkens IA, Lynch L, Mehalek KE, Berkowitz GS, Berkowitz RL. Efficacy and side effects of magnesium sulfate and ritodrine as tocolytic agents. *American Journal of Obstetrics and Gynecology* 1988; **159**: 685–689.
4. Karedoff MN, Roak ER, Datta SJ. Hypermagnesaemia and anaesthetic management. *Canadian Anaesthetists Society Journal* 1982; **29**: 35–41.
5. Hart DM. Heartburn in pregnancy. *Journal of Internal Medicine Research* 1978; **6** (Suppl.): 1–5.
6. Davison JS, Davison MC, Hay DM. Gastric emptying time in late pregnancy and labour. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970; **77**: 37–41.
7. Attia RR, Ebeid AM, Fischer JE, Goudsouzian NG. Maternal–fetal and placental gastrin concentrations. *Anaesthesia* 1982; **37**: 18–21.
8. McGoldrick KE. Anesthesia and the eye. In: Barash PG, Cullen BF, Stoelting RS, eds. *Clinical Anesthesia*, 2nd Edn. Philadelphia: JP Lippincott Co, 1992; 1095–1112.
9. Pandey K, Badolas RP, Lumar S. Time course of intraocular hypertension produced by suxamethonium. *British Journal of Anaesthesia* 1972; **44**: 191–196.
10. Lincoff HA, Ellis CH, Devoe AG, DeBeer EJ, Impastato DJ, Berg S, Orkin L, Magda H. Effect of succinylcholine on intraocular pressure. *American Journal of Ophthalmology* 1955; **40**: 501–510.
11. Meyers EF, Krupin T, Johnson M, Zink H. Failure of nondepolarizing blockers to inhibit succinylcholine-induced increased intraocular pressure: A controlled study. *Anesthesiology* 1978; **48**: 149–151.
12. Agoston Sandor, Vandenbrom RHG, Wierda JMKH. Clinical pharmacokinetics of neuromuscular blocking drugs. *Clinical Pharmacokinetics* 1992; **22**: 94–115.
13. Huizinga ACT, Vandenbrom RHG, Wierda JMKH, Hommes FDM, Hennis PJ. Intubating conditions and onset of neuromuscular block of rocuronium (Org 9426); a comparison with suxamethonium. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 463–468.
14. Tryba M, Zorn A, Thole H, Zenz M. Rapid-sequence orotracheal intubation with rocuronium: A randomized double-blind comparison with suxamethonium—preliminary communication. *European Journal of Anaesthesiology* 1994; **11** (Suppl. 9): 44–48.
15. Abouleish E, Abboud T, Lechevalier T, Zhu J, Chalian A, Alford K. Rocuronium (Org 9426) for Caesarean section. *British Journal of Anaesthesia* 1994; **73**: 336–341.
16. Robertson EN, Hull JM, Verbeek AM, Booij LHDJ. A comparison of rocuronium and vecuronium: The pharmacodynamic, cardiovascular and intra-ocular effects. *European Journal of Anaesthesia* 1994; **11** (Suppl. 9): 116–121.
17. De Mey JC, Debrock M, Rolly G. Evaluation of the onset and intubation conditions of rocuronium bromide. *European Journal of Anaesthesia* 1994; **11** (Suppl. 9): 37–40.
18. Naguib M. Different priming techniques, including mivacurium, accelerate the onset of rocuronium. *Canadian Journal of Anaesthesia* 1994; **41**: 902–907.
19. Ghoneim MM, Long JP. Interaction between magnesium and other neuromuscular blocking agents. *Anesthesiology* 1970; **32**: 23–27.
20. del-Castillo J, Engback L. The nature of neuromuscular block produced by magnesium. *Journal of Physiology (London)* 1954; **124**: 370–384.
21. van den Broek I, Wierda JMKH, Smeulers NJ, van Santen GJ, Leclercq MGL, Hennis PJ. Clinical pharmacology of rocuronium (Org 9426): Study of the time course of action, dose requirement, reversibility, and pharmacokinetics. *Journal of Clinical Anesthesia* 1994; **6**: 288–296.
22. Liu PL, Warren TM, Ostheimer GW, Weiss JB, Liu LMP. Foetal monitoring in parturients undergoing surgery unrelated to pregnancy. *Canadian Anaesthetists Society Journal* 1985; **32**: 525–532.

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Isoflurane for sedation in a case of congenital myasthenia gravis

C. McBeth and T. G. L. Watkins

Summary

We describe the use of isoflurane for the management of a 3-yr-old boy with congenital myasthenia gravis who required ventilation for pneumonia. While in the intensive care unit he was sedated with isoflurane for 5 days (81 MAC-h). This provided a safe, easily controllable method of sedation which avoided the use of neuromuscular blocking agents and appeared to have no significant side effects during use. However, after it was stopped the patient developed a fine, self-limiting tremor which lasted for 2 days. Previous reports of paediatric patients sedated with isoflurane suggest that prolonged exposure may result in temporary dose-dependent neurological dysfunction, including hallucinations, ataxia and non-purposeful movements. (*Br. J. Anaesth.* 1996; **77**: 672–674)

Key words

Anaesthetics volatile, isoflurane. Complications, myasthenia gravis.

Myasthenia gravis is an acquired autoimmune disorder which is caused by a decrease in functioning postsynaptic acetylcholine receptors at the neuromuscular junction caused by their destruction or inactivation by circulating antibodies.[1 2] The disease is characterized by muscle fatigue and weakness which is exacerbated by repeated use and which recovers partially with rest. It particularly affects ocular, pharyngeal and laryngeal muscles (bulbar muscles) but may also involve proximal and distal limb muscles and respiratory muscles.[3 4]

Congenital myasthenia is an extremely rare form of the disease which presents during the first few years of life and is usually of autosomal recessive inheritance.[5] Anti-acetylcholine receptor antibodies are absent, and defective neuromuscular transmission may be a result of a variety of different causes, including acetylcholinesterase deficiency, defective resynthesis or vesicular packaging of acetylcholine, or lack of acetylcholine receptors.[5–7] Myasthenic patients are exquisitely sensitive to non-depolarizing neuromuscular blocking agents[2 3 9 10] and use of these agents should generally be avoided.[2 11]

Isoflurane has been used successfully to sedate paediatric patients in the intensive care unit. The low blood-gas solubility (blood-gas partition coefficient 1.4) allows rapid change in the level of sedation and rapid awakening when sedation has been stopped. It does not appear to have significant adverse effects on cardiovascular, renal or hepatic function[12]; however there have been some reports of temporary neurological dysfunction after prolonged sedation with isoflurane. Three cases of peripheral neuropathy which resolved spontaneously have been described in adults.[13 14] In one this was accompanied by flaccid paralysis of all four limbs which lasted for 3 months. In children, agitation, hallucinations and non-purposeful movements which resolved over 72 h have been seen after sedation with isoflurane.[15 16] We describe the use of isoflurane for sedation in a case of congenital myasthenia gravis.

Case report

A boy aged 2 yr 6 months, weighing 19.3 kg, first presented in January 1995 with a short history of choking on solids, dysarthria and partial ptosis of his right eyelid. His mother noted that he had suffered frequent falls. On examination, he had obvious ptosis which was partially compensated for by a head tilt. There was rapid resolution of the ptosis and dysarthria after administration of edrophonium 100 $\mu g\ kg^{-1}$ i.v. Serology was negative for anti-acetylcholine receptor antibodies. A diagnosis of congenital myasthenia gravis was made and oral pyridostigmine commenced at a dose of 1 mg kg^{-1}, five times per day.

He remained well until November 1995 when he developed a cough, pyrexia and vomiting, and as a result became increasingly weak because of failure to absorb oral pyridostigmine. He had a poor cough and was unable to clear secretions adequately. On examination, ventilatory frequency was 60 bpm, heart rate 140 beat min^{-1} and oxygen saturation 88% breathing air. On auscultation of the chest there were widespread coarse crepitations, particularly on the left side. His chest x-ray showed evidence of left-sided pneumonia with almost complete opacification of the left hemithorax, loss of volume and shift of the mediastinum to the left. He was commenced on antibiotic therapy, oxygen via a high-flow fixed-performance face mask and physiotherapy, but over

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the course of the next few hours became increasingly tired and unable to maintain satisfactory oxygen saturation breathing 60% oxygen. He was admitted to the intensive care unit for ventilation. His trachea was intubated with a 5-mm nasal tracheal tube after inhalation induction with increasing concentrations of isoflurane in 100% oxygen. His lungs were ventilated with 1.5% isoflurane in a mixture of oxygen and air via a circle system using a Roche 3100S ventilator. Total fresh gas flow was 2 litre min^{-1}. End-tidal isoflurane concentration was not measured. The inspired isoflurane concentration (range 1–2.5%) was adjusted to maintain a sedation score of 4–5 on a six-point scale modified from Ramsay and colleagues,[17] and was increased intermittently to enable physiotherapy, suctioning and other procedures to be tolerated.

Pneumonia was treated with cefotaxime 150 mg kg^{-1} day^{-1} i.v., erythromycin 100 mg kg^{-1} day^{-1} i.v. and regular physiotherapy. Erythromycin was stopped the following day because of concern about potential interference with neuromuscular transmission in myasthenic patients.[18] Nasogastric pyridostigmine 1 mg kg^{-1}, 5 times per day, was continued throughout the illness.

By day 5 in the intensive care unit his pneumonia had resolved and his clinical condition had stabilized. A total of 81 MAC-h of isoflurane[19] had been administered. At this stage, isoflurane was stopped and within 15 min the patient was awake and able to respond to commands. He opened his eyes fully, squeezed fingers to command with a strong grip and was able to lift his head off the pillow for a sustained length of time. After breathing 35% oxygen spontaneously via the tracheal tube for 40 min, his arterial blood-gas tensions were satisfactory (pH 7.55, $P\mathrm{CO}_2$ 4.3 kPa, $P\mathrm{O}_2$ 22 kPa, base excess +6.5 mmol litre^{-1}, saturation 99%) and his trachea was extubated uneventfully.

He remained in the intensive care unit breathing 28% oxygen via a face mask for another 46 h during which time he was noted to have a fine tremor. This affected all limbs, was not worsened by intentional movement and disappeared on sleeping. His axillary temperature was 36.5 °C and his metabolic and electrolyte status were normal. The tremor did not require treatment and had disappeared by the time the patient returned to the paediatric ward 2 days later. He was discharged home after 1 week.

Discussion

Congenital myasthenia consists of several extremely rare genetically determined defects, manifest as variable muscle weakness from birth.[2 5–7] It rarely presents in the neonatal period but more commonly during the first 1–2 yr of life. Antibodies to the acetylcholine receptor cannot be demonstrated and a variety of pre- and postsynaptic defects have been described.[5–7] The course of the disease tends to be non-fluctuating and compatible with long survival. As the disease is not autoimmune in nature, steroids and immunosuppressants are ineffective and treatment consists primarily of anticholinesterases. Congenital myasthenia is not to be confused with neonatal myasthenia which is seen in infants of myasthenic mothers and presents at birth. It is thought to be caused by the passage of anti-acetylcholine receptor antibodies across the placenta.[2]

In our case there was no family history of myasthenia gravis or consanguinity, and the patient's sister, who was 1 yr older, showed no sign of disease. In addition, he was antibody-negative but responded to edrophonium, indicating a diagnosis of congenital myasthenia, although the actual structural or electrophysiological abnormality has not yet been defined.

Management of patients with myasthenia gravis who require an anaesthetic or ventilation is problematic; not only does the disease itself lead to a decrease in functioning acetylcholine receptors so the response to both depolarizing and non-depolarizing neuromuscular blocking agents is abnormal,[8–10 20 21] but drugs used to treat the disease also affect the response, and therefore interpretation is difficult. Anticholinesterases inhibit plasma cholinesterase[22 23] and hence hydrolysis of suxamethonium.[24–26] In contrast, inhibition of acetylcholinesterase by anticholinesterases may in theory increase the need for non-depolarizing neuromuscular blocking agents although in practice this has not been documented.[24] As a result, different anaesthetic techniques are described which either aim to reduce the dose of neuromuscular blocking agents or avoid their use.[11 27] In addition, the disease primarily affects bulbar muscles and those of respiration and therefore the patient's ability to swallow, cough, maintain their own airway and breathe adequately is already compromised and assessment of whether or not a patient's trachea is ready to be extubated may be difficult. Clinical assessment of the patient's ability to sustain a head lift off the pillow, generate a negative inspiratory pressure of more than 25 cm H_2O and spontaneously maintain a tidal volume of more than 5 ml kg^{-1} is useful, combined with arterial blood-gas analysis to ensure that oxygenation is adequate and $P\mathrm{CO}_2$ does not exceed 6.6 kPa.[11]

In an attempt to avoid using opioids, neuromuscular blockers or cumulative doses of sedatives, we sedated this patient with isoflurane. Myasthenic patients experience some depression of neuromuscular function with isoflurane, but this does not appear to be clinically significant at concentrations of 1.5% or lower and recovery is rapid.[27 28] Isoflurane has been used for sedation in both adult and paediatric intensive care units.[13 29 30] The low blood-gas solubility and low lipid solubility allow the level of sedation to be titrated easily without drug accumulation so that patients wake up quickly when isoflurane is stopped.[30] There do not appear to be significant cardiovascular or hepatic side effects,[12 15] but concern has been voiced over the potential for nephrotoxicity. Although there have been reports of serum fluoride concentrations exceeding 50 μmol litre^{-1} in patients requiring prolonged sedation with isoflurane, none has suggested isoflurane-induced renal dysfunction.[31 32] Several reports have mentioned the occurrence of neurological dysfunction after sedation with isoflurane. In adults, three cases of peripheral neuropathy have been described.[13, 14] Two patients sedated with isoflurane for 151 and 254 h developed peripheral neuropathies which lasted 4–12 months.[13] A third patient was sedated with 1.5% isoflurane for 9 days and developed a distal sensory neuropathy on day 15 associated with decreased joint position and vibration sense which had disappeared 2 days later. At the same time, this patient developed flaccid paralysis of all four limbs, with absent reflexes. Management was supportive and recovery almost complete by 3 months.[14]

There have also been reports of neurological dysfunction in children. In one report, five of 10 children sedated with at least 70 MAC-h of isoflurane developed agitation and non-purposeful movements.[15] In another, 12 of 29 children developed ataxia, agitation, hallucinations and confusion after 0.25–1.5% isoflurane for 24–76 h. These symptoms had disappeared spontaneously by 72 h.[16] The observations in both of these reports are complicated by the fact that all children had also received opioids and benzodiazepines while in the intensive care unit, and therefore it is difficult to be certain that isoflurane was responsible for the symptoms. The mechanism by which the neurological abnormalities are caused has not yet been satisfactorily explained.[14, 16, 33] Our patient did not receive any other sedatives or hypnotics, however his underlying disease process may have been wholly or partly responsible for the tremor.

References

1. Newsom-Davis J. Disorders of neuromuscular transmission. In: Weatherall D J, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine.* Oxford: Oxford Medical Publications, 1996; 4164.
2. Baraka A. Anaesthesia and myasthenia gravis. *Canadian Journal of Anaesthesia* 1992; **39**: 476–486.
3. Loh L. Neurological and neuromuscular disease. *British Journal of Anaesthia* 1986; **58**: 180–200.
4. Skin and musculoskeletal diseases. In: Stoelting RK, Dierdorf SF, eds. *Anesthesia and Co-Existing Disease,* 3rd Edn. Edinburgh: Churchill Livingstone, 1993; 439–443.
5. Triggs WJ, Beric A, Butler IJ, Roongta SM. A congenital myasthenic syndrome refractory to acetylcholinesterase inhibitors. *Muscle and Nerve* 1992; **15**: 267–272.
6. Engel AG, Nagel A, Walls TJ, Harper CM, Waisburg HA. Congenital myasthenic syndromes: I. Deficiency and short open-time of the acetylcholine receptor. *Muscle and Nerve* 1993; **16**: 1284–1292.
7. Uchitel O, Engel AG, Walls TJ, Nagel A, Atassi MZ, Bril V. Congenital myasthenic syndromes: II. Syndrome attributed to abnormal interaction of acetylcholine with its receptor. *Muscle and Nerve* 1993; **16**: 1293–1301.
8. Ward S ,Wright DJ. Neuromuscular blockade in myasthenia gravis with atracurium besylate. *Anaesthesia* 1984; **39**: 51–53.
9. Hunter JM, Bell CF, Florence AM, Jones RS, Utting JE. Vecuronium in the myasthenic patient. *Anaesthesia* 1985; **40**: 848–853.
10. Seigne RD, Scott RPF. Mivacurium chloride and myasthenia gravis. *British Journal of Anaesthesia* 1994; **72**: 468–469.
11. El-Dawlatly AA, Ashour MH. Anaesthesia for thymectomy in myasthenia gravis: a non-muscle-relaxant technique. *Anaesthesia and Intensive Care* 1994; **22**: 458–460.
12. Willats SM, Spencer EM. Sedation for ventilation in the critically ill. A role for isoflurane? *Anaesthesia* 1994; **49**: 422–428.
13. Millane TA, Bennett ED, Grounds RM. Isoflurane and propofol for long term sedation in the intensive care unit. A crossover study. *Anaesthesia* 1992; **47**: 768–774.
14. Du Peloux Menage H, Duffy S, Yates DW, Hughes JA. Reversible sensorimotor impairment following prolonged ventilation with isoflurane and vecuronium for acute severe asthma. *Thorax* 1992; **47**: 1078–1079.
15. Arnold JH, Truog RD, Rice SA. Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. *Anesthesia and Analgesia* 1993; **76**: 520–526.
16. Kelsall AWR, Ross-Russell R, Herrick MJ. Reversible neurologic dysfunction following isoflurane sedation in pediatric intensive care. *Critical Care Medicine* 1994; **22**: 1032–1034.
17. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone–alphadolone. *British Medical Journal* 1974; **2**: 656–659.
18. May EF, Calvert PC. Aggravation of myasthenia gravis by erythromycin. *Annals of Neurology* 1990; **28**: 577–579.
19. Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children. *Anesthesia and Analgesia* 1984; **63**: 418–420.
20. Vanlinthout LEH, Robertson EN, Booij LHDJ. Response to suxamethonium during propofol–fentanyl–N_2O/O_2 anaesthesia in a patient with active myasthenia gravis receiving long-term anticholinesterase therapy. *Anaesthesia* 1994; **49**: 509–511.
21. Eisenkraft JB, Book WJ, Mann SM, Papatestas AE, Hubbard M. Resistance to succinylcholine in myasthenia gravis: a dose response study. *Anesthesiology* 1988; **69**: 760–763.
22. Baraka A, Wakid N, Mansour R, Haddad W. Effect of neostigmine and pyridostigmine on the plasma cholinesterase activity. *British Journal of Anaesthesia* 1981; **53**: 849–851.
23. Baraka A. Suxamethonium–neostigmine interaction in patients with normal or atypical cholinesterase. *British Journal of Anaesthesia* 1977; **49**: 479–483.
24. Baraka A, Baroody M, Yazbeck V. Repeated doses of suxamethonium in the myasthenic patient. *Anaesthesia* 1993; **48**: 782–784.
25. Baraka A. Suxamethonium block in the myasthenic patient. *Anaesthesia* 1992; **47**: 217–219.
26. Miller J, Lee C. Muscle diseases. In: Katz J, Benumof J, Kadis LB, eds. *Anesthesia and Uncommon Diseases.* Philadelphia: Saunders, 1981; 552.
26. Rowbottom S J. Isoflurane for thymectomy in myasthenia gravis. *Anaesthesia and Intensive Care* 1989; **17**: 444–447.
27. Eisenkraft JB, Papatestas AE, Sivak M. Neuromuscular effects of halogenated agents in patients with myasthenia gravis. *Anesthesiology* 1984; **61**(3A): A307.
29. Breheny FX, Kendall PA. Use of isoflurane for sedation in intensive care. *Critical Care Medicine* 1992; **20**: 1062–1064.
30. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. *British Medical Journal* 1989; **298**: 1277–1280.
31. Spencer EM, Willatts SM, Prys-Roberts C. Plasma inorganic fluoride concentrations during and after prolonged (>24h) isoflurane sedation: effect on renal function. *Anesthesia and Analgesia* 1991; **73**: 731–737.
32. Murray JM, Trinick TR. Plasma fluoride concentrations during and after prolonged anesthesia: a comparison of halothane and isoflurane. *Anesthesia and Analgesia* 1992; **74**: 236–240.
33. Antognini JF. Neurologic dysfunction after isoflurane sedation. *Critical Care Medicine* 1995; **23**: 789.

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Orthotopic liver transplantation in two patients with hypertrophic obstructive cardiomyopathy

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Summary

Orthotopic liver transplantation (OLT) in patients with end-stage liver disease is a procedure associated with high cardiac output, low systemic vascular resistance (SVR), coagulopathy and the potential for significant blood loss. A feature of hypertrophic obstructive cardiomyopathy (HOCM) is left ventricular outflow tract obstruction which may be exacerbated by reduced SVR, reduced filling pressures, tachycardia and positive inotropy. We report two cases of OLT in patients with HOCM. Our anaesthetic technique involved the use of halothane and vecuronium and avoidance of drugs causing tachycardia and positive inotropy. Management was aided by intraoperative transoesophageal echocardiography which showed that filling pressures poorly reflected end-diastolic volumes. Volume administration, vasoconstrictors and avoidance of inotropes and chronotropes reduced the outflow tract obstruction which was particularly severe in the reperfusion period. (*Br. J. Anaesth.* 1996; **77**: 675–677)

Key words
Monitoring, echocardiography. Surgery, hepatic. Liver, transplantation. Complications, hypertrophic obstructive cardiomyopathy.

Case reports

CASE NO. 1

The patient was a 46-yr-old male with end-stage alcoholic liver disease. He had portal hypertension with severe ascites, oesophageal varices and impaired renal function. Clotting function tests showed mild coagulopathy (international normalized ratio (INR) 1.5). Preoperative transoesophageal echocardiography (TOE) was performed to evaluate a murmur heard on physical examination. It showed asymmetrical septal hypertrophy, systolic anterior motion (SAM) of the mitral valve with normal mitral morphology, mild mitral regurgitation (MR) and left ventricular outflow tract (LVOT) obstruction, and a resting gradient 36 mm Hg (fig. 1) and thus a diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) was made. After nitrate provocation there was increased SAM, severe MR and an LVOT gradient of 64 mm Hg.

Anaesthesia was induced with fentanyl 6 $\mu g\ kg^{-1}$ and thiopentone 100 mg and maintained with fentanyl 3 $\mu g\ kg^{-1}\ h^{-1}$ and halothane in air and oxygen. Neuromuscular block was produced with vecuronium. Monitoring included an oximetric pulmonary artery catheter and TOE. During liver resection a baseline TOE was performed and fluid challenges were given to assess changes in left ventricular (LV) dimensions. Full cardiopulmonary bypass with heparin-bonded tubing was on standby.

Haemodynamic variables at various times are shown in table 1.

During the anhepatic stage the patient developed a low systemic vascular resistance index (SVRI) and increased cardiac index (CI). Fibrinolysis was demonstrated by a decrease in euglobulin clot lysis time and fibrinogen concentration, and 7 litre of blood were lost over 120 min. An infusion of phenylephrine was commenced and fluid was replaced according to LV dimensions on TOE rather than pulmonary capillary wedge pressure (PCWP). Veno–venous bypass (femoro–portal to axillary vein) was used electively during the anastomosis of the new liver.

On reperfusion the patient developed severe reperfusion syndrome. He also developed a severe coagulopathy and another 15 litre of blood was lost in the first hour after reperfusion. Total intraoperative blood loss was 42 litre. Vasodilatation and blood loss were associated with an increase in the severity of the LVOT obstruction measured on TOE. TOE also showed a relatively empty LV with dynamic systolic function (in spite of a PCWP of 30 mm Hg), increased SAM, severe LVOT obstruction (maximum measured gradient 120 mm Hg) and severe MR. This was treated with aggressive volume replacement and infusion of phenylephrine. Inotropes were avoided.

In the 3 h after reperfusion the degree of outflow obstruction reduced gradually as SVRI increased. His postoperative course was relatively uneventful and he was well 18 months after transplant.

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Table 1 Haemodynamic variables at five times during operation. III-5 = 5 min before reperfusion during the anhepatic phase, III+5 = 5 min after reperfusion, III+60 = 60 min after reperfusion, and III+180 = 180 min after reperfusion

Stage	Heart rate (beat min^{-1})	MAP (mm Hg)	CI (litre min^{-1} m^{-2})	SVRI (dyn s m^{-2} cm^{-5})	PCWP (mm Hg)
Patient 1					
Baseline	98	74	4.4	1239	10
III-5	86	57	5.3	840	12
III+5	86	49	6.8	460	20
III+60	106	56	6.8	538	30
III+180	116	61	5.7	736	15
Patient 2					
Baseline	95	68	8.4	560	16
III-5	114	76	9.7	530	13
III+5	115	69	12.0	346	23
III+60	107	70	10.6	474	24
III+180	114	76	9.5	541	16

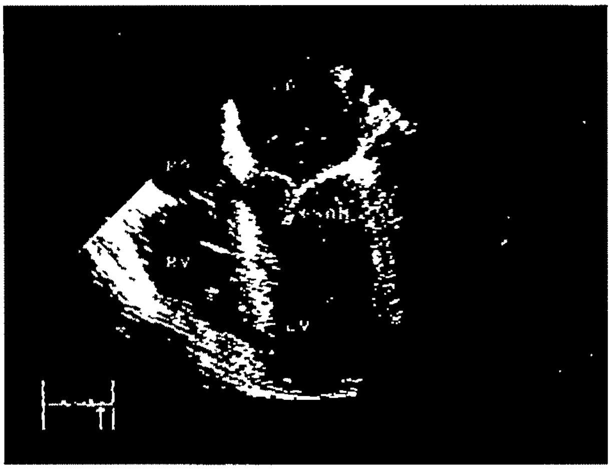

Figure 1 Patient No. 1. Transoesophageal four-chamber view showing septal hypertrophy and systolic anterior motion of the mitral valve. LA = Left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, SAM = systolic anterior motion of the mitral valve.

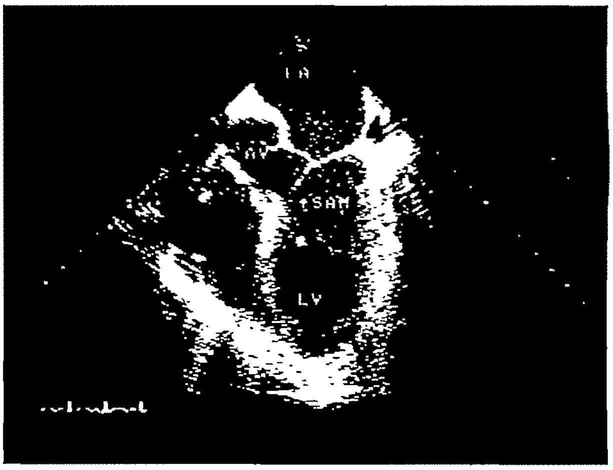

Figure 2 Patient No. 2. Transoesophageal modified four-chamber view showing small left ventricular cavity, severe systolic anterior motion of the mitral valve and almost complete obliteration of the left ventricular outflow tract (peak gradient 120 mm Hg). This was accompanied by severe mitral regurgitation on colour flow Doppler (not shown). AV = Aortic valve. Other abbreviations as in figure 1.

CASE NO. 2

The patient was a 32-yr-old female with a 16-yr history of autoimmune chronic active hepatitis. She was jaundiced, markedly cushingoid and had severe hepato–pulmonary syndrome with cyanosis and clubbing. She was an insulin-dependent diabetic secondary to steroid administration. Her renal function was normal and preoperative clotting tests showed mild coagulopathy (INR 2.0). She had a murmur but no symptoms of HOCM. Preoperative transthoracic echocardiography and TOE demonstrated severe concentric left ventricular hypertrophy, normal mitral morphology and mild SAM associated with moderate MR and an LVOT gradient of 60 mm Hg without provocation.

Anaesthesia was induced with thiopentone 250 mg and fentanyl 8 μg kg^{-1} and maintained with fentanyl 3 μg kg^{-1} h^{-1} and halothane in air and oxygen. Neuromuscular block was produced with vecuronium. Monitoring included TOE and an oximetric pulmonary artery catheter. After induction of anaesthesia, derived cardiac indices showed a hyperdynamic circulation (see table 1). However, TOE showed only mild to moderate SAM and MR and the LVOT gradient was only 12 mm Hg. Cardiac output was maintained during a 5-min trial of inferior vena cava (IVC) occlusion and therefore a decision was made to perform the proximal anastomosis without bypass. The IVC was cross-clamped for 13 min in total. Later in the anhepatic stage, TOE showed mild SAM, mild MR but an increasingly hyperdynamic left ventricle with worsening LVOT obstruction. SVRI decreased from 900 to 530 dyn s m^2 cm^{-5}. An infusion of phenylephrine was therefore started and extra fluids were given in addition to replacement of minimal blood loss.

With reperfusion SVRI decreased to 346 dyn s m^2 cm^{-5}. Transoesophageal echocardiography showed development of marked SAM with severe MR and LV cavity obliteration during systole (fig. 2) The maximal LVOT gradient measured was 64 mm Hg. Multiple boluses and increasing rates of infusion of phenylephrine were administered. Washed donor red cells (600 ml) and Haemaccel 1 litre were infused in the first 30 min after reperfusion, despite minimal blood loss, in an attempt to increase ventricular volumes and reduce LV systolic obliteration as seen on TOE. PCWP increased to 24 mm Hg and CI increased to 10.61 min^{-1} m^{-2} but LV obliteration and outflow tract obstruction changed little.

Slowly over 2 h LVOT obstruction and MR and SAM resolved to levels similar to those in the pre-anhepatic stage. One hour after reperfusion an infusion of prostaglandin E_1 (PGE_1) 10 $\mu g\ h^{-1}$ was started, slowly increasing to 30 $\mu g\ h^{-1}$ as the patient's vasodilatation allowed.

The patient's postoperative course was complicated only by minor sepsis and transient pancytopenia. She was well 1 yr after transplant and her hepato-pulmonary syndrome is resolving.

Discussion

Hypertrophic cardiomyopathy (HCM) is inappropriate myocardial hypertrophy often involving the septum of a non-dilated left ventricle. HOCM is a subset of HCM in which the hypertrophy causes LVOT obstruction. It is an autosomal dominant condition with variable penetrance.[1]

The features of HOCM are a hypercontractile left ventricle, diastolic dysfunction, a high ejection fraction and systolic anterior motion of the mitral valve with or without mitral regurgitation. The obstruction is dynamic in that it changes depending on preload, afterload, sympathetic activity and posture.

The symptoms of HOCM range from none to dyspnoea, syncope, palpitations, chest pain and sudden death. Signs include a jerky pulse, fourth heart sound and an early to mid-systolic murmur increasing with a Valsalva manoeuvre. Diagnosis is usually confirmed by echocardiography.

The problems of providing anaesthesia to a patient with HOCM are exacerbated in liver transplantation. Patients with liver disease tend to have a low systemic vascular resistance and liver transplantation is associated with further vasodilatation, the potential for significant blood loss and occasionally the need for inotropes around the time of reperfusion. All of these factors exacerbate the haemodynamic disturbances of HOCM, which benefits from high afterload and preload, a relatively low heart rate and negative inotropy. Diastolic function is markedly impaired in HOCM and delayed isovolumetric relaxation reduces early diastolic filling.[2 3] There is an increased reliance on atrial contraction, diastolic filling pressures and adequate duration of diastolic filling.[4]

We chose an anaesthetic technique that avoided drugs such as isoflurane and pancuronium which cause vasodilatation and tachycardia and instead used halothane and vecuronium. We used phenylephrine for vasoconstriction as it has no inotropic or chronotropic effect. Our unit routinely administers PGE_1 to all liver transplant patients in the post-reperfusion period to increase hepatic blood flow and for its presumed cytoprotective effect. In case No. 1 we were unable to begin PGE_1 infusion, a potent vasodilator, until the patient had returned to the ICU, because of his extreme peripheral vasodilatation. In case No. 2 the patient tolerated only a very slow increase in the infusion rate to 30 $\mu g\ h^{-1}$ in theatre.

Transoesophageal echocardiography played a very important role in the intraoperative management of both patients. The measured haemodynamics of high PCWP and low mean arterial pressure, especially in the post-reperfusion period, may have prompted the use of inotropic agents with their potentially deleterious effects. However, TOE demonstrated low ventricular volumes despite a high PCWP and management was therefore with additional fluids and a direct acting vasopressor (phenylephrine). It has been shown during OLT that TOE has a better correlation with ventricular volumes than does PCWP.[5–8] In this case we found TOE to be the most useful guide to fluid management, especially in the post-reperfusion period.

References

1. Maron BJ, Bonow RO, Cannon RO, Leon MB, Epstein SE. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology and therapy (1). *New England Journal of Medicine* 1987; **316**: 780–789.
2. Sanderson JE, Traill TA, St John Sutton MG, Brown DJ, Gibson DG, Goodwin JF. Left ventricular relaxation and filling in hypertrophic cardiomyopathy. *British Heart Journal* 1978; 40: 596–601.
3. Spirito P, Maron BJ, Chiarella F, Bellotti P, Tramarin R, Pollozi M, Vecchio C. Diastolic abnormalities in patients with hypertrophic cardiomyopathy: relation to magnitude of left ventricular hypertrophy. *Circulation* 1985; 72: 310–316.
4. Bonow R, Frederick T, Bacharach S, Green M, Goose P, Maron B, Rosing DR. Atrial systole and left ventricular filling in hypertrophic cardiomyopathy: effect of verapamil. *American Journal of Cardiology* 1983; 51: 1386–1391.
5. Ellis JE, Lichtor JL, Feinstein SB, Chung MR, Polk SL, Broelsch C, Emond J, Thistlewaite JR, Roizen MF. Right heart dysfunction, pulmonary embolus and paradoxical embolization during liver transplantation: A transesophageal two-dimensional echocardiographic study. *Anesthesia and Analgesia* 1989; **68**: 777–782.
6. Stelzer H, Blezek G, Gabriel A, Leitner K, Mayer N, Müller C, Tüchy GL, Zimpfer M. Two-dimensional transesophageal echocardiography in early diagnosis and treatment of hemodynamic disturbances during liver transplantation. *Transplantation Proceedings* 1991; 23: 1957–1958.
7. de la Morena G, Acosta F, Villegas M, Olivares A, Contreras RF, Bueno FS, Sanchez-Muñoz J, Ruiperez JA, Parrilla P. Transesophageal echocardiographic evaluation of left ventricular function during orthotopic liver transplantation. *Transplantation Proceedings* 1993; 25: 1832.
8. Tüchy GL, Gabriel A, Müller H, Tüchy B, Naderer M, Stelzer C, Zimpfer M. Titrating the preload by using the rapid infusion system: use of echocardiography during orthotopic liver transplantation. *Transplantation Proceedings* 1993; 25: 1858–1860.

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COMMENTARY

Permissive hypercapnia and gas exchange in lungs with high $\dot{Q}s/\dot{Q}t$: a mathematical model

C. J. JOYCE AND K. G. HICKLING

Summary

Low volume ventilation with permissive hypercapnia is becoming widely used in the treatment of acute respiratory distress syndrome. A mathematical model was developed to examine the effects of hypoventilation on pulmonary gas exchange in lungs with a range of shunt fractions. Hypoventilation did not worsen gas exchange, provided the inspired oxygen concentration was high enough to maintain PA_{O_2} at an adequate level. In lungs with a high shunt fraction, some improvement in gas exchange may result, but these effects are small. A rightwards shift of the oxygen–haemoglobin dissociation curve induced by hypercapnia, is likely to be beneficial rather than detrimental in patients with acute respiratory distress syndrome. This analysis was limited to the direct effects of hypoventilation in lungs with constant shunt fractions, and did not encompass a number of possible secondary effects such as changes in cardiac output with Pa_{CO_2}, changes in shunt fraction associated with a reduction in mean airway pressure and possible direct effects of hypercapnia on the pulmonary vasculature or airways. (*Br. J. Anaesth.* 1996; **77**: 678–683)

Key words
Carbon dioxide, hypercapnia. Carbon dioxide, ventilatory response. Lung, shunting. Ventilation, hypoventilation. Model, matematical.

Animal models have suggested that orthodox mechanical ventilation during acute respiratory distress syndrome (ARDS), with high peak inspiratory pressures, may result in additional lung injury and possibly remote organ dysfunction. Low volume ventilation with permissive hypercapnia may avoid this ventilator-induced lung injury.[1] However, it has been suggested that the rightward shift of the oxygen–haemoglobin dissociation curve caused by hypercapnia may be detrimental in ARDS, as arterial oxygen content may be reduced more than venous oxygen unloading is facilitated.[2] A theoretical mathematical model was developed to investigate the effects of hypercapnia on pulmonary gas exchange in lungs with high levels of intrapulmonary shunt.

Methods

GENERAL DESCRIPTION

The aim of the model was to describe the effect of hypoventilation on steady state pulmonary gas exchange in lungs with varying degrees of intrapulmonary shunt. The lung was modelled as consisting of two compartments (see fig. 1). One compartment was perfused by mixed venous blood and not ventilated; the other compartment was both perfused and ventilated. It was assumed that the partial pressures of oxygen and carbon dioxide in blood leaving the ventilated lung unit had equilibrated with the lung unit, and that metabolic oxygen consumption and carbon dioxide production by the lung tissue were negligible. The peripheral tissues were modelled as a single compartment, with oxygen consumption and carbon dioxide production determined by the model. Tissue metabolism was modelled in two different ways. In the "constant metabolism" version of the model, $\dot{V}O_2$ was set at 250 ml (STPD)/min and $\dot{V}CO_2$ was set at 200 ml (STPD)/min. These values were maintained constant. In the "constant $P\bar{v}_{O_2}$" version, $P\bar{v}_{O_2}$ was maintained constant as might occur when tissue utilization of oxygen is limited by oxygen delivery, and the respiratory quotient was maintained constant at 0.8.

Pulmonary gas exchange was examined by calculating alveolar, arterial and mixed venous partial pressures and contents of oxygen and carbon dioxide for a range of input variables. The input variables FI_{O_2}, Pa_{CO_2}, P_{50}, $\dot{Q}$ and $\dot{Q}s/\dot{Q}t$ (and $P\bar{v}_{O_2}$ in the constant $P\bar{v}_{O_2}$ model) were specified and held constant during each set of calculations. In the model, P_{50} is defined as the partial pressure of oxygen necessary to 50% saturate haemoglobin at pH 7.4, PCO_2 5.33 kPa and 37 °C.

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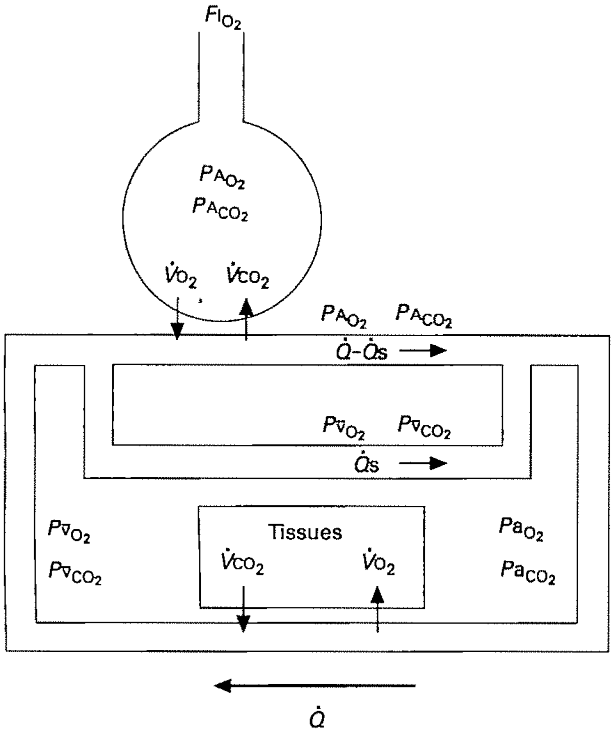

Figure 1 A model of the effect of hypercapnia on gas exchange.

MATHEMATICAL ANALYSIS

When the input variables were specified, there was a unique set of alveolar, arterial and mixed venous partial pressures and contents of oxygen and carbon dioxide that satisfied the constraints of a particular version of the model. Thus $Pa_{O_2} = f$ (FI_{O_2}, Pa_{CO_2}, P_{50}, $\dot{Q}$, $\dot{Q}s/\dot{Q}t$). To simplify calculations in the program, this was re-expressed as $FI_{O_2} = g$ (Pa_{O_2}, Pa_{CO_2}, P_{50}, $\dot{Q}$, $\dot{Q}s/\dot{Q}t$). As the other variables in this function are specified and held constant, this function can be solved for Pa_{O_2} using the false position method.[3] This method uses a trial value of Pa_{O_2} and calculates the corresponding value of FI_{O_2}, then uses this information to generate a better estimate of the Pa_{O_2} corresponding to the desired value of FI_{O_2}, with iteration until the desired precision is obtained (desired value of FI_{O_2} ± 0.00002 in this study). When the solution for Pa_{O_2} is obtained, other values of interest (Ca_{O_2}, Ca_{CO_2}, $C\bar{v}_{O_2}$, $C\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$ are readily calculated. Details of the model equations are in appendix 1.

Both the constant metabolism model and the constant $P\bar{v}_{O_2}$ model were used to study scenarios with P_{50} = 3.57 kPa, over a range of $\dot{Q}$ values from 2.5 to 10 litre min^{-1}, Pa_{CO_2} from 1.33 to 94.64 kPa, FI_{O_2} from 0.21 to 1.0 and $\dot{Q}s/\dot{Q}t$ from 0.05 to 0.8. In the constant $P\bar{v}_{O_2}$ model, a range of $P\bar{v}_{O_2}$ values from 1.33 to 8.00 kPa were studied. In the constant metabolism model, a range of P_{50} from 2.45 to 3.57 kPa, and the effect of varying $\dot{Q}$ as a function of Pa_{CO_2} were studied (see appendix 2). The programs performing these analyses were written using Think Pascal (Symantec) and run on a Macintosh Centris.

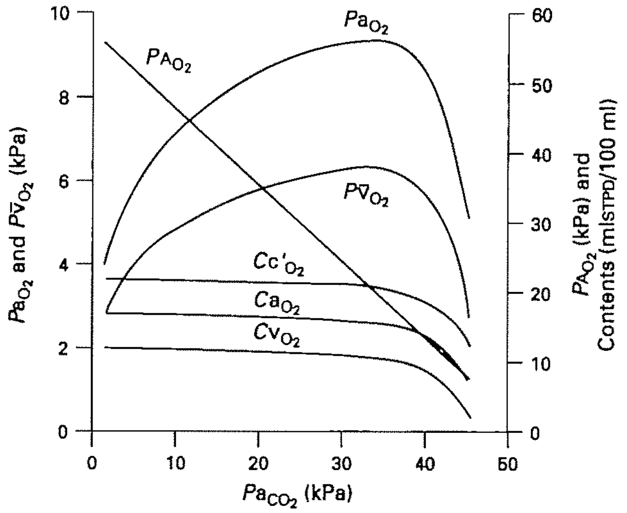

Figure 2 Constant metabolism model: effects of Pa_{CO_2}. Input variables are FI_{O_2} = 0.6, $\dot{Q}s/\dot{Q}t$ = 0.5, P_{50} = 3.57, $\dot{Q}$ = 5 litre min^{-1}. In this figure (and fig. 8) the range of Pa_{CO_2} is 0–50 kPa, while in all other figures only the clinical range of 0–20 kPa is shown.

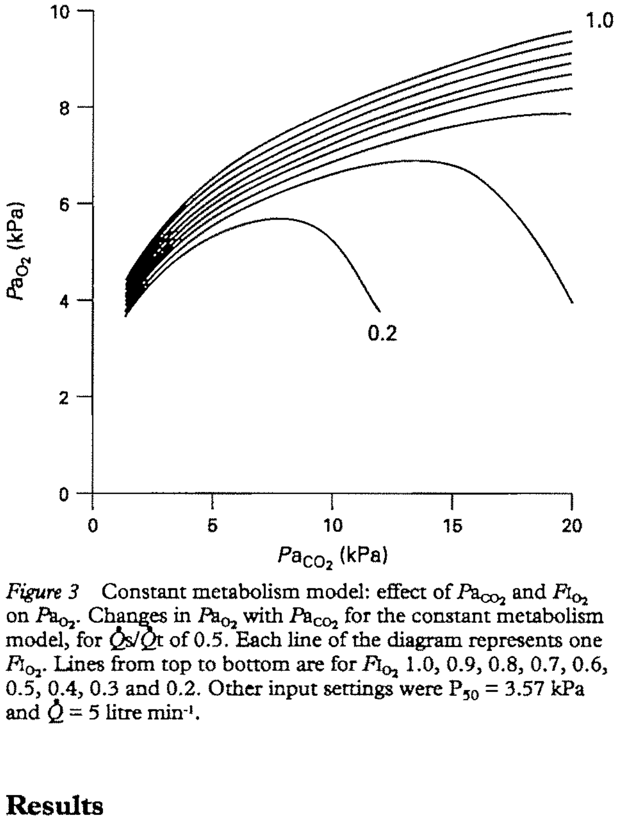

Figure 3 Constant metabolism model: effect of Pa_{CO_2} and FI_{O_2} on Pa_{O_2}. Changes in Pa_{O_2} with Pa_{CO_2} for the constant metabolism model, for $\dot{Q}s/\dot{Q}t$ of 0.5. Each line of the diagram represents one FI_{O_2}. Lines from top to bottom are for FI_{O_2} 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3 and 0.2. Other input settings were P_{50} = 3.57 kPa and $\dot{Q}$ = 5 litre min^{-1}.

Results

CONSTANT METABOLISM MODEL

The effect on oxygen carriage, of increasing Pa_{CO_2} when other input variables are held constant, is shown in figure 2. As Pa_{CO_2} increases, there is a linear decrease in PA_{O_2} caused by increasing PA_{CO_2}. This has minimal effect on Cc'_{O_2} (and hence Ca_{O_2} and $C\bar{v}_{O_2}$), until PA_{O_2} decreases below a threshold level and desaturation of haemoglobin in blood leaving the ventilated lung compartment begins. Up to this point, the rightward shift of the dissociation curve, in the presence of relatively constant Ca_{O_2} and $C\bar{v}_{O_2}$, produces an increase in Pa_{O_2} and $P\bar{v}_{O_2}$. Beyond this point, Cc'_{O_2}, Ca_{O_2}, $C\bar{v}_{O_2}$, Pa_{O_2} and $P\bar{v}_{O_2}$

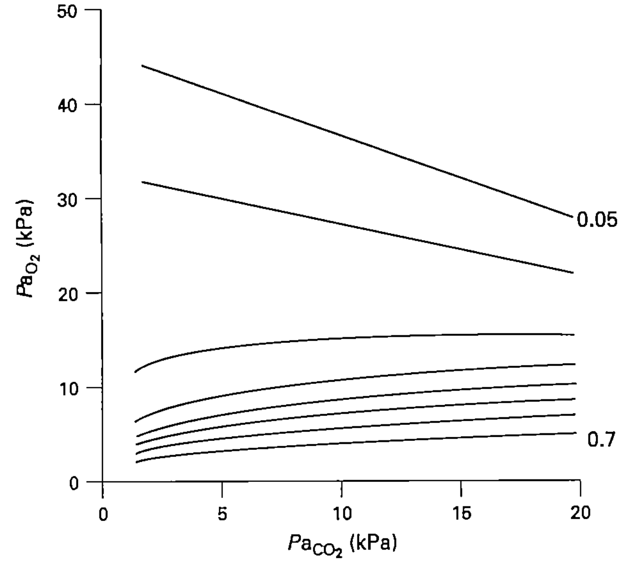

Figure 4 Constant metabolism model: effect of Pa_{CO_2} and $\dot{Q}s/\dot{Q}t$ on Pa_{O_2}. Changes in Pa_{O_2} with Pa_{CO_2} for the constant metabolism model, for FI_{O_2} of 0.6. Each line on the diagram represents one $\dot{Q}s/\dot{Q}t$. Lines from top to bottom are for $\dot{Q}s/\dot{Q}t$ 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.7. Other input settings were P_{50} = 3.57 kPa and $\dot{Q}$ = 5 litre min^{-1}. In this figure the range of Pa_{O_2} is 0–50 kPa, while in all other figures 0–10 kPa is shown.

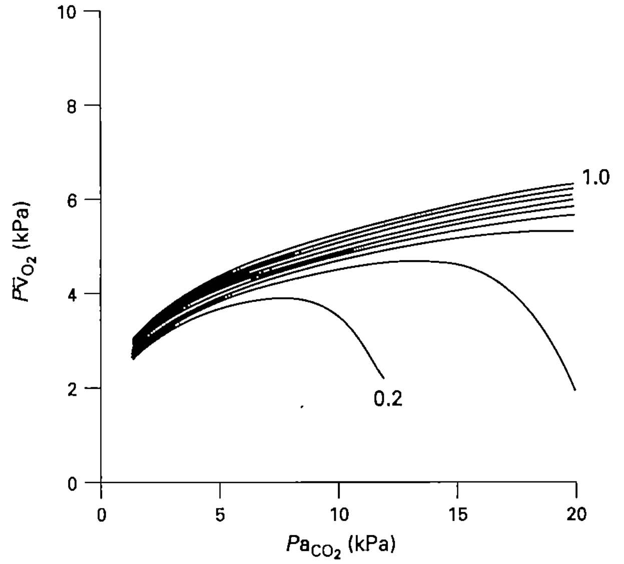

Figure 5 Constant metabolism model: effect of Pa_{CO_2} and FI_{O_2} on $P\bar{v}_{O_2}$. Changes in $P\bar{v}_{O_2}$ with Pa_{CO_2} for the constant metabolism model, for $\dot{Q}s/\dot{Q}t$ of 0.5. Each line of the diagram represents one FI_{O_2}. Lines from top to bottom are for FI_{O_2} 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3 and 0.2. Other input settings were P_{50} = 3.57 kPa and $\dot{Q}$ = 5 litre min^{-1} (as in fig. 3).

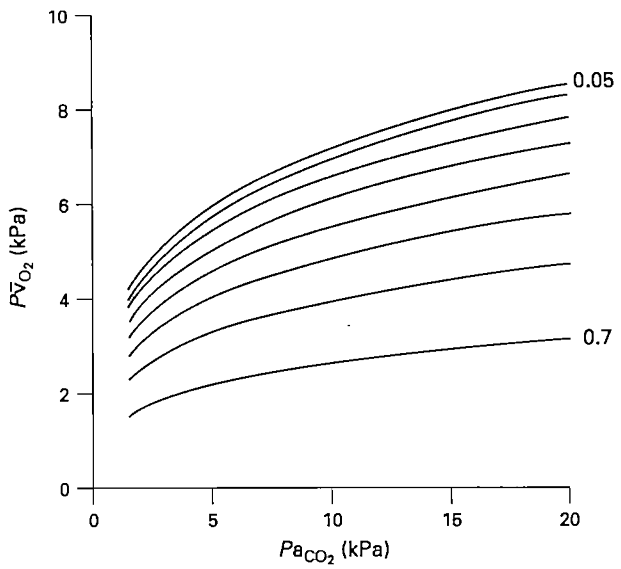

Figure 6 Constant metabolism model: effect of Pa_{CO_2} and $\dot{Q}s/\dot{Q}t$ on $P\bar{v}_{O_2}$. Changes in $P\bar{v}_{O_2}$ with Pa_{CO_2} for the constant metabolism model, for FI_{O_2} of 0.6. Each line on the diagram represents one $\dot{Q}s/\dot{Q}t$. Lines from top to bottom are for $\dot{Q}s/\dot{Q}t$ 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.7. Other input settings were P_{50} = 3.57 kPa and $\dot{Q}$ = 5 litre min^{-1} (as in fig. 4).

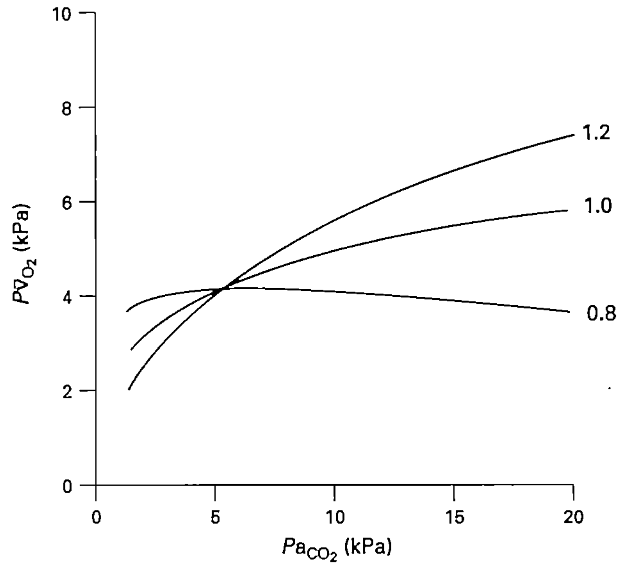

Figure 7 Constant metabolism model: effect on $P\bar{v}_{O_2}$ of varying $\dot{Q}$ with Pa_{CO_2}. Changes in $P\bar{v}_{O_2}$ with Pa_{CO_2} for the constant metabolism model. Other input settings were P_{50} = 3.57 kPa, FI_{O_2} = 0.6 and $\dot{Q}s/\dot{Q}t$ 0.5.

decrease. The PA_{CO_2} at which this threshold is reached varies with FI_{O_2} (figs 3 and 5). The pattern of change in Pa_{O_2} as Pa_{CO_2} increases is different with low $\dot{Q}s/\dot{Q}t$ values (0.05 or 0.1) when Pa_{O_2} decreases in a similar manner to PA_{O_2} (see fig. 4). With low values of $\dot{Q}s/\dot{Q}t$ the reduction in dissolved oxygen in blood leaving the ventilated lung compartment more than offsets the effect on Pa_{O_2} of the right shifted oxygen–haemoglobin dissociation curve, because the ventilated compartment represents most of the lung. With $\dot{Q}s/\dot{Q}t$ = 0, Pa_{O_2} is identical to PA_{O_2}.

Figures 5 and 6 show the changes in $P\bar{v}_{O_2}$ over a range of Pa_{CO_2}. For all $\dot{Q}s/\dot{Q}t$, $P\bar{v}_{O_2}$ increases as Pa_{CO_2} increases, provided that FI_{O_2} is adequate to maintain PA_{O_2} above the threshold level for haemoglobin desaturation (fig. 6). If FI_{O_2} is not adequate, then the threshold level for haemoglobin desaturation is exceeded within the clinical range of Pa_{CO_2}, and $P\bar{v}_{O_2}$ decreases (fig. 5).

A similar pattern of results was seen with P_{50} values of 2.45 and 3.05 kPa. A lower P_{50} resulted in lower Pa_{O_2} and $P\bar{v}_{O_2}$ at a given Pa_{CO_2}, when the other variables were held constant. With an FI_{O_2} of 0.6, $\dot{Q}s/\dot{Q}t$ of 0.5 and $\dot{Q}$ of 5 litre min^{-1}, at any given Pa_{CO_2} in the range 0–20 kPa, the $P\bar{v}_{O_2}$ result for P_{50} of 2.45 kPa was 69–71% of the $P\bar{v}_{O_2}$ result for a P_{50} of 3.57 kPa.

Similar results were seen with $\dot{Q}$ values of 2.5 and 10 litre min^{-1}. A lower $\dot{Q}$ resulted in lower Pa_{O_2} and $P\bar{v}_{O_2}$ at a given Pa_{CO_2}, when the other variables were held constant. When $\dot{Q}$ was varied as a function of Pa_{CO_2} the pattern was different (fig. 7). Relatively small changes in $\dot{Q}$ (20% decrease in $\dot{Q}$ for a doubling in Pa_{CO_2}) virtually abolished any increase in $P\bar{v}_{O_2}$ with increasing Pa_{CO_2}, and marked decreases in $P\bar{v}_{O_2}$ were seen within the range of Pa_{CO_2} used clinically during low volume ventilation with permissive hypercapnia (Pa_{CO_2} of 5.33–20 kPa).

Hypocapnia consistently made gas exchange worse. In all the scenarios modelled, $P\bar{v}_{O_2}$ decreased as Pa_{CO_2} decreased to less than 5.3 kPa. When the shunt fraction was high, Pa_{O_2} also decreased (fig. 4).

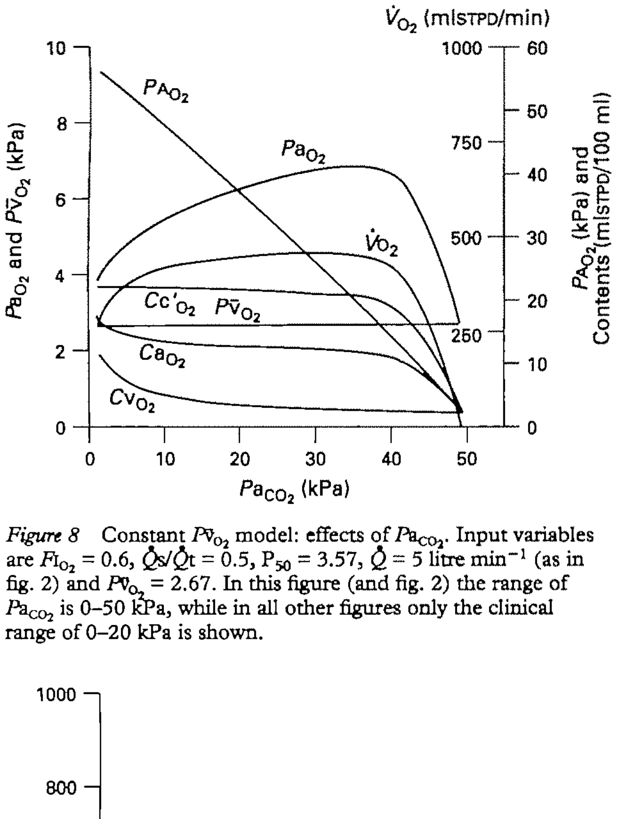

Figure 8 Constant $P\bar{v}_{O_2}$ model: effects of Pa_{CO_2}. Input variables are FI_{O_2} = 0.6, $\dot{Q}s/\dot{Q}t$ = 0.5, P_{50} = 3.57, $\dot{Q}$ = 5 litre min^{-1} (as in fig. 2) and $P\bar{v}_{O_2}$ = 2.67. In this figure (and fig. 2) the range of Pa_{CO_2} is 0–50 kPa, while in all other figures only the clinical range of 0–20 kPa is shown.

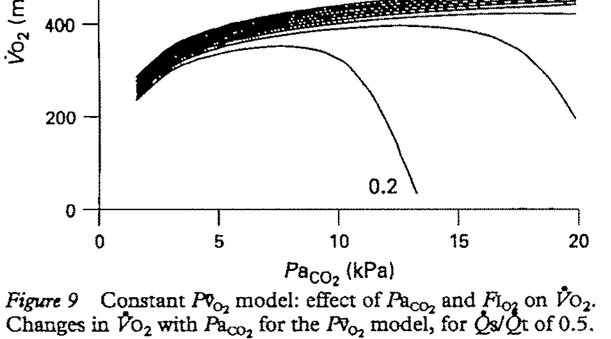

Figure 9 Constant $P\bar{v}_{O_2}$ model: effect of Pa_{CO_2} and FI_{O_2} on $\dot{V}O_2$. Changes in $\dot{V}O_2$ with Pa_{CO_2} for the $P\bar{v}_{O_2}$ model, for $\dot{Q}s/\dot{Q}t$ of 0.5. Each line of the diagram represents one FI_{O_2}. Lines from top to bottom are for FI_{O_2} 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3 and 0.2. Other input settings were P_{50} = 3.57 kPa, $\dot{Q}$ = 5 litre min^{-1} and $P\bar{v}_{O_2}$ = 2.67.

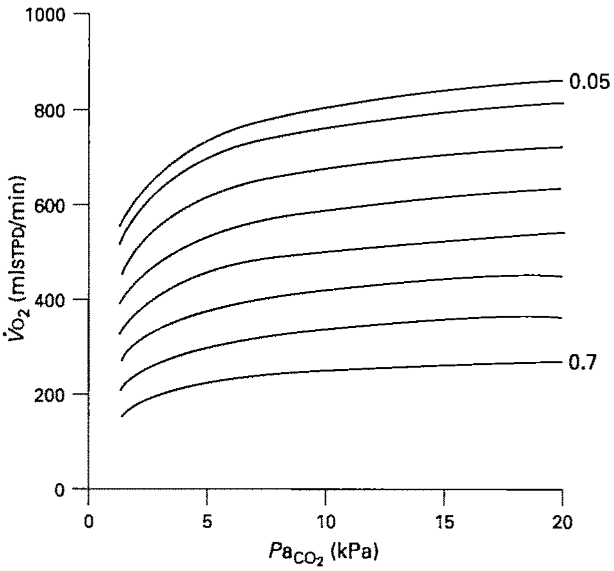

Figure 10 Constant $P\bar{v}_{O_2}$ model: effect of Pa_{CO_2} and $\dot{Q}s/\dot{Q}t$ on $\dot{V}O_2$. Changes in $\dot{V}O_2$ with Pa_{CO_2} for the constant $P\bar{v}_{O_2}$ model, for FI_{O_2} of 0.6. Each line on the diagram represents one $\dot{Q}s/\dot{Q}t$. Lines from top to bottom are for $\dot{Q}s/\dot{Q}t$ 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.7. Other input settings were P_{50} = 3.57 kPa, $\dot{Q}$ = 5 litre min^{-1} and $P\bar{v}_{O_2}$ = 2.67.

CONSTANT $P\bar{v}_{O_2}$ MODEL

The effect on $\dot{V}O_2$ and oxygen carriage of increasing Pa_{CO_2} when other input variables are held constant is shown in figure 8. The increase in Pa_{CO_2} produced an increase in $P\bar{v}_{CO_2}$. The model defines $P\bar{v}_{O_2}$ as constant, so Cv_{O_2} decreases as the increasing $P\bar{v}_{CO_2}$ shifts the dissociation curve to the right. As Pa_{CO_2} increases, there is a linear decrease in PA_{O_2} caused by increasing PA_{CO_2}. This has minimal effect on Cc'_{O_2}, until PA_{O_2} decreases below a threshold level and desaturation of haemoglobin in blood leaving the ventilated lung compartment begins. Ca_{O_2} is determined by mixing of constant proportions of blood with Cc'_{O_2} and Cv_{O_2}. Up to the threshold point, Cc'_{O_2} is relatively constant. Thus as Cv_{O_2} decreases, Ca_{O_2} also decreases but not to the same extent as Cv_{O_2}. The difference between Ca_{O_2} and Cv_{O_2} widens and hence $\dot{V}O_2$ increases. Another effect of the widening difference between Ca_{O_2} and Cv_{O_2} as Pa_{CO_2} increases is that with similar increases in PCO_2 in both arterial and venous blood, and hence similar rightward shift of the two dissociation curves, the difference between Pa_{O_2} and $P\bar{v}_{O_2}$ also increases, and Pa_{O_2} must increase as $P\bar{v}_{O_2}$ is held constant. Beyond the threshold point, $\dot{V}O_2$, Pa_{O_2}, Cc'_{O_2}, Ca_{O_2} and Pa_{O_2} decrease. The pattern of change in Pa_{O_2} as Pa_{CO_2} increases is different with low $\dot{Q}s/\dot{Q}t$ when Pa_{O_2} decreases in a similar manner to PA_{O_2}.

Figures 9 and 10 show the changes in $\dot{V}O_2$ over a range of Pa_{CO_2}. For all $\dot{Q}s/\dot{Q}t$, $\dot{V}O_2$ increases as Pa_{CO_2} increases, provided that FI_{O_2} is adequate to maintain PA_{O_2} above the threshold level for haemoglobin desaturation (fig. 10). If FI_{O_2} is not adequate, then the threshold level for haemoglobin desaturation is exceeded within the clinical range of Pa_{CO_2}, and $\dot{V}O_2$ decreases (fig. 9).

A similar pattern of results was seen with $P\bar{v}_{O_2}$ set at 1.33, 4.00 or 5.33 kPa, and with P_{50} values of 2.45 and 3.05 kPa. A lower $P\bar{v}_{O_2}$ resulted in a higher $\dot{V}O_2$ when the other input variables were unchanged. The greatest improvement in $\dot{V}O_2$ with increasing Pa_{CO_2} occurred when $P\bar{v}_{O_2}$ was high. With $P\bar{v}_{O_2}$ of 1.33 kPa there was a minimal decrease in $\dot{V}O_2$ when Pa_{CO_2} increased to greater than 17 kPa. A lower P_{50} resulted in a lower $\dot{V}O_2$ for any given Pa_{CO_2}. As can be predicted from the equations of the model, any increase in $\dot{Q}$ simply increased $\dot{V}O_2$ by the same factor.

As with the constant metabolism model, hypocapnia consistently made gas exchange worse. In all scenarios modelled, $\dot{V}O_2$ decreased as Pa_{CO_2} decreased to less than 5.3 kPa.

Discussion

It has been suggested that a rightward shift of the dissociation curve may be detrimental in ARDS, because reduction of arterial oxygen content may more than offset the amount by which venous oxygen unloading is facilitated.[2] In a pig model of hypoxaemia caused by low inspired oxygen concentration, and hypercapnia produced by high inspired carbon dioxide concentration, arterial oxygen content was increased and mortality reduced when acidosis was partially corrected by buffering. It was postulated that buffering had reduced the right shift of the dissociation curve thus improving pulmonary oxygen uptake.[2] In rats breathing air at reduced atmospheric pressure, survival was improved with a left-shifted oxygen dissociation curve.[4] A theoretical study suggested that a left shift of the oxygen dissociation curve may improve exercise tolerance at high altitude, if diffusion limitation of oxygen uptake is present.[5] However, these studies examined the response to alteration in P_{50} with hypoxaemia caused by low PA_{O_2}. In this situation it is the low PA_{O_2} which limits oxygen uptake by pulmonary blood flow and determines Pa_{O_2}. A right-shifted dissociation curve then results in decreased arterial oxygen content at this limited Pa_{O_2}, and is thus potentially detrimental. Hypercapnia has an additional detrimental effect in that it further decreases PA_{O_2}.

In contrast, when hypoxaemia results from intrapulmonary shunt, PA_{O_2} in ventilated lung remains high even with moderately high Pa_{CO_2} provided that the inspired oxygen concentration is sufficiently high. Under these conditions, blood leaving the ventilated lung compartment is fully saturated, and arterial oxygen content is determined by the shunt fraction and venous oxygen content. The effect of a right-shifted dissociation curve is then to increase Pa_{O_2} associated with this predetermined arterial oxygen content. If cardiac output and oxygen consumption do not change, then mixed venous oxygen content is unaltered and $P\bar{v}_{O_2}$ also increases. Our mathematical model confirms that in patients with pure intrapulmonary shunt causing hypoxaemia who are receiving a sufficiently high inspired oxygen concentration to ensure full saturation of the pulmonary blood flow in the ventilated lung compartment, and with other variables remaining constant, acute hypercapnia should result in an increase in Pa_{O_2} and $P\bar{v}_{O_2}$ with little change in arterial and mixed venous oxygen contents. If the increase in $P\bar{v}_{O_2}$ allows greater oxygen uptake into hypoxic tissues, this could theoretically increase tissue oxygen utilization, and the model predicts that potentially important increases could result. Our model suggests that reversing the rightwards shift of the dissociation curve by buffering may be detrimental to gas exchange.

In reality the situation is more complex, and several of the variables which were assumed to remain constant in this model may alter in patients with ARDS during low volume ventilation with permissive hypercapnia. Alterations in cardiac output affect gas exchange. Acute hypercapnia depresses the contractility of isolated myocardium,[6] although this is compensated rapidly during sustained hypercapnia, as a result of correction of intracellular acidosis.[7] *In vivo*, decreased contractility is offset by increased sympathetic stimulation, and cardiac output increases.[8] Recent studies of patients with ARDS have found that cardiac output increased in all patients during low volume ventilation with permissive hypercapnia.[9–11]

The shunt fraction may also be affected by several factors during low volume ventilation with permissive hypercapnia, including changes in mean airway pressure,[12] changes in cardiac output[13 14] and direct or autonomically mediated effects on the pulmonary vasculature or the airways.

Our model assumes that either oxygen consumption or carbon dioxide production is constant or limited by the lowest $P\bar{v}_{O_2}$ at which tissues can extract oxygen, but it is likely that acute hypercapnia has important metabolic effects. The resulting intracellular acidosis alters the activity of several enzymes, for example phosphofructokinase. Conversely, increased sympathetic activity and increased endogenous catecholamine concentrations may increase metabolic rate and $\dot{V}O_2$.

Buffering may be detrimental to gas exchange by reversing the rightwards shift of the dissociation curve and by inhibiting the potentiation of hypoxic pulmonary vasoconstriction caused by acidosis.[15] The metabolic compensation that occurs during prolonged hypercapnia shifts the curve to the left and worsens gas exchange.

Several studies have demonstrated that in patients with ARDS, hypoxaemia appears to be predominantly a result of intrapulmonary shunt,[9 16] and therefore the findings of this study should be applicable to such patients. However, there is some variability in the proportion of intrapulmonary shunt and $\dot{V}/\dot{Q}$ inequality between patients, and in those with a substantial proportion of low $\dot{V}/\dot{Q}$ regions the model is inaccurate. Another limitation of this study is that the Kelman subroutines used to calculate oxygen contents and tensions have been validated only up to a $P\text{CO}_2$ value of 20 kPa.[17] While the results at higher partial pressures are inaccurate, the results are valid over the range of Pa_{CO_2} values used in clinical practice.

The constant $P\bar{v}_{O_2}$ model examines the situation where oxygen delivery to the tissues is inadequate, so that oxygen is extracted from the blood down to a limiting level of $P\bar{v}_{O_2}$. Below a $P\bar{v}_{O_2}$ value of 2.67 kPa tissue oxygenation may be inadequate for cellular function. Our data show the level of oxygen consumption that can be supported at this $P\bar{v}_{O_2}$ value. Patients with ARDS and sepsis often have high oxygen consumption, and it has been suggested that even with normal values for oxygen delivery, oxygen uptake may be limited by its delivery to the tissues.[18]

Thus the physiological consequences and interactions after the reduction of ventilatory support and onset of hypercapnia are extremely complex, and may vary substantially between patients. Further studies of the effects of hypercapnia are needed. However, this study suggests that the effect of the right-shifted dissociation curve *per se* in patients with ARDS is likely to be beneficial rather than detrimental.

Appendix 1

MODEL EQUATIONS

Procedure used for calculating FI_{O_2} for a trial value of Pa_{O_2}

1. Ca_{CO_2} and Ca_{O_2} are calculated from Pa_{CO_2} and the trial value of Pa_{O_2} using West's modifications of Kelman's subroutines.[17 19–21]

2. *In the "constant metabolism" version of the model*

Cv_{CO_2} and Cv_{O_2} are calculated by

$$Cv_{CO_2} = Ca_{CO_2} + (\dot{V}CO_2/\dot{Q})$$

$$Cv_{O_2} = Ca_{O_2} - (\dot{V}O_2/\dot{Q})$$

In the "constant $P\bar{v}_{O_2}$" version of the model

As Ca_{O_2}, Ca_{CO_2} and $P\bar{v}_{O_2}$ are known, there is a unique set of $P\bar{v}_{CO_2}$, Cv_{CO_2} and Cv_{O_2} that will satisfy the constraint of the model that RQ = 0.8

where $RQ = (Cv_{CO_2} - Ca_{CO_2})/(Ca_{O_2} - Cv_{O_2})$. Thus $RQ = f(P\bar{v}_{CO_2})$, and $P\bar{v}_{CO_2}$ is solved by the false position method. Cv_{CO_2} and Cv_{O_2} are calculated from $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$ using Kelman's subroutines.

3. The contents of carbon dioxide and oxygen in blood equilibrated with the ventilated compartment are calculated by $Cc'_{O_2} = (Ca_{CO_2} - Cv_{CO_2} \times \dot{Q}s/\dot{Q}t)/(1 - \dot{Q}s/\dot{Q}t)$

$$Cc'_{O_2} = (Ca_{O_2} - Cv_{O_2} \times \dot{Q}s/\dot{Q}t)/(1 - \dot{Q}s/\dot{Q}t)$$

4. $P\mathrm{A}_{CO_2}$ and $P\mathrm{A}_{O_2}$ are calculated from Cc'_{CO_2} and Cc'_{O_2}, using Kelman's subroutines and the false position method.

5. FI_{O_2} is calculated by

$$FI_{O_2} = (P\mathrm{A}_{O_2} + (P\mathrm{A}_{CO_2}/RQ))/((PB - PH_2O) + (P\mathrm{A}_{CO_2}/RQ)\,(1 - RQ))$$

(This equation was derived by algebraic manipulation of the alveolar gas equation).

Constants used in these calculations were haemoglobin = 15 g dl^{-1}, packed cell volume = 0.45, base excess = 0 mmol $litre^{-1}$, temperature = 37.0 °C, PB = 101.3 kPa, $SVP_{(H_2O)} = 6.26$ kPa, RQ = 0.8.

Final calculations

When the solution of Pa_{O_2} for the specified value of FI_{O_2} has been found, then Ca_{O_2}, Ca_{CO_2}, Cv_{O_2}, Cv_{CO_2}, Cc'_{O_2}, Cc'_{CO_2}, $P\mathrm{A}_{O_2}$ and $P\mathrm{A}_{CO_2}$ are calculated as above in steps 1 to 4. $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$ are calculated from Cv_{O_2} and Cv_{CO_2} using Kelman's subroutines and the false position method.

Appendix 2

METHOD OF VARYING $\dot{Q}$ AS A FUNCTION OF Pa_{CO_2}

The effect of varying $\dot{Q}$ as a function of Pa_{CO_2} was investigated. Calculations of the constant metabolism model were followed, except that the $\dot{Q}$ to be used with the other input variables was calculated from the Pa_{CO_2}, by the equation

$$\dot{Q} = \dot{Q}5.33\ \Theta(\log_2(Pa_{CO_2}/5.33))$$

where $\dot{Q}5.33$ is cardiac output at $Pa_{CO_2} = 5.33$ kPa and is set at 5 litre min^{-1}. This equation produces an increase in $\dot{Q}$ by a factor of Θ for each doubling of Pa_{CO_2}. Thus $\dot{Q}5.33 = 5$ litre min^{-1}, $\dot{Q}10.66 = 5\Theta$ litre min^{-1}, and $\dot{Q}21.32 = 5\Theta^2$ litre min^{-1}. Values of Θ examined were 0.8, 1.0 and 1.2.

References

1. Hickling KG. Low volume ventilation with permissive hypercapnia in the adult respiratory distress syndrome. *Clinical Intensive Care* 1992; **3**: 67–78.
2. Wetterberg T, Sjoberg T, Steen S. Effects of buffering in hypercapnia and hypercapnic hypoxaemia. *Acta Anaesthesiologica Scandinavica* 1993; 37: 343–349.
3. Shoup TE. *Applied Numerical Methods for the Microcomputer.* Englewood Cliffs, New Jersey: Prentice-Hall, 1984.
4. Eaton JW, Skelton TD, Berger E. Survival at extreme altitude: protective effect of increased haemoglobin–oxygen affinity. *Science* 1974; **183**: 743–744.
5. Bencowitz HZ, Wagner PD, West J. Effect of change of P_{50} on exercise tolerance at high altitude: a theoretical study. *Journal of Applied Physiology* 1982; 53: 1487–1495.
6. Tang W, Weil MH, Gazmuri RJ. Reversible impairment of myocardial contractility due to hypercarbic acidosis in the isolated perfused rat heart. *Critical Care Medicine* 1991; **19**: 218–224.
7. Foex P, Fordham RMM. Intrinsic myocardial recovery from the negative inotropic effects of acute hypercapnia. *Cardiovascular Research* 1972; **6**: 257–262.
8. Cullen DJ, Eger EI. Cardiovascular effects of carbon dioxide in man. *Anesthesiology* 1974; 41: 345–349.
9. Langeron O, Delclaux C, Roupie E. Haemodynamics and gas exchange alterations due to permissive hypercapnia in human ARDS: a multiple inert gas elimination technique (MIGET) study. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: A420.
10. Puybasset L, Stewart T, Rouby JJ. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance injuced by permissive hypercapnia in patients with acute respiratory distress syndrome. *Anesthesiology* 1994; **80**: 1254–1267.
11. Thorens JB, Chopard P, Jolliet JC, Chevrolet JC. Effect of permissive hypercapnia on tissue oxygenation in acute respiratory failure. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**: A68.
12. Marcy TW, Marini JJ. Inverse ratio ventilation in ARDS—Rationale and implementation. *Chest* 1991; **100**: 494–504.
13. Breen PH, Schumaker PT, Sandoval J. Increased cardiac output increases shunt: Role of pulmonary edema and perfusion. *Journal of Applied Physiology* 1985; **59**: 1313–1321.
14. Freden F, Cigarini I, Mannting F. Dependence of shunt on cardiac output in unilobar oleic acid edema: Distribution of ventilation and perfusion. *Intensive Care Medicine* 1993; **19**: 185–190.
15. Brimioulle S, Vachiery JL, Lejeune P, Leeman M, Melot C, Naeije R. Acid–base status affects gas exchange in canine oleic-acid pulmonary edema. *American Journal of Physiology (Heart Circulation Physiology 29)* 1991; **260**: H1086.
16. Dantzker DR, Brook CJ, Dehart P. Ventilation–perfusion distributions in the adult respiratory syndrome. *American Review of Respiratory Disease* 1979; **120**: 1039–1052.
17. Kelman GR. Computer program for the production of O_2–CO_2 diagrams. *Respiration Physiology* 1968; **4**: 260–269.
18. Samsel RW, Schumacker PT. Oxygen delivery to tissues. *European Respiratory Journal* 1991; **4**: 1258–1267.
19. Kelman GR. Calculation of certain indices of cardiopulmonary function using a digital computer. *Respiration Physiology* 1966; **1**: 335–343.
20. Kelman GR. Digital computer procedure for the conversion of PCO_2 into blood CO_2 content. *Respiration Physiology* 1967; **3**: 111–115.
21. West JB, Wagner PD. Pulmonary gas exchange. In: J.B. West, eds. *Bioengineering Aspects of the Lung.* New York: Marcel Decker, Inc., 1977; 363–369.

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ABSTRACTS

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BIRMINGHAM MEETING

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(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Performance of vaporizers in circle systems [III]

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When vaporizers are used within circle systems, the temperature within the vaporizer decreases as the agent evaporates. This reduces the output of the vaporizer and may be of clinical importance.

We investigated this effect both on the bench and in theatre using a Komesaroff vaporizer, a copy of the Goldman into which a thermometer may be placed. All tests were conducted using isoflurane, the vaporizer being filled to the 30 ml level before each experiment. On the bench, gas flow rates of 4, 8 and 12 litre min^{-1} were passed through the vaporizer and the changes in temperature of the isoflurane were recorded. The greatest decrease in temperature was seen with a flow rate of 12 litre min^{-1}, the temperature decreasing from 20 to 0°C within 18 min with the vaporizer open at setting 3.

In theatre, the vaporizer was attached on the inspiratory side of a Scania circle system. Isoflurane temperature was measured at 1-min intervals using a thermistor and a record of the ambient temperatures at the start and finish of the case were made. Patients were anaesthetized with propofol and allowed to breathe spontaneously on a laryngeal mask airway. We found that the temperature in the vaporizer was related to both the vaporizer setting and the patient's minute volume. Initially, on a high inspired isoflurane concentration, the temperature decreased quite quickly, but as the anaesthetic continued and the vaporizer setting was reduced, the temperature increased (fig. 1). Also shown are minor fluctuations in isoflurane temperature related to episodes where the patient's minute volume increased in response to surgical stimulus and decreased after administration of i.v. opioids.

The maximum reduction in temperature can be calculated, using the Antoine equation, to produce a maximum reduction in isoflurane concentration of 48%. This effect is not found to be a problem in clinical practice owing to the previously described self-regulating properties of this system.[1]

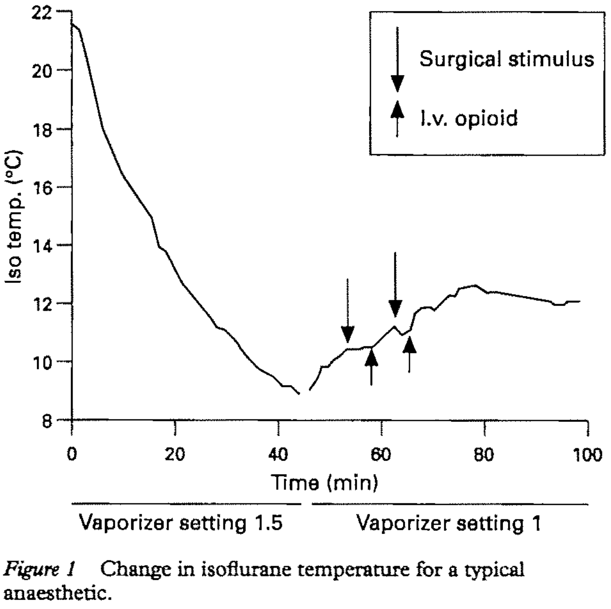

Figure 1 Change in isoflurane temperature for a typical anaesthetic.

Key words
Equipment, circle system. Equipment, vaporizers.

Reference

1. Worthington L, Royston B, White D. *British Journal of Anaesthesia* 1995;75: 228P.

Pharmacodynamics of Org 9487: onset and recovery characteristics of single and three incremental bolus doses

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The need for a non-depolarizing neuromuscular blocking agent with onset and recovery characteristics similar to suxamethonium is recognized. Early reversal of residual block using an anticholinesterase would be an attractive feature of such an agent; it would be useful if attempts at tracheal intubation failed. Org 9487, the 16-*N*-allyl-β-propionate analogue of vecuronium, is a new aminosteroid neuromuscular blocking agent.[1] We compared recovery from profound block using neostigmine or edrophonium, after either a single bolus dose or a bolus plus three maintenance doses of Org 9487.

Twenty-four patients, ASA I–III, were recruited to the study. They were allocated randomly to one of four groups: Groups la and lb received neostigmine 0.05 mg kg^{-1}, la after a single bolus of Org 9487 and lb after three maintenance doses; Groups 2a and 2b were similarly reversed with edrophonium 1.0 mg kg^{-1}. Patients received lorazepam 2–4 mg orally, 2 h before operation. After induction of anaesthesia with midazolam 0.05–0.1 mg kg^{-1}, fentanyl 1–3 μg kg^{-1} and thiopentone 4–6 mg kg^{-1}, anaesthesia was maintained with nitrous oxide 70% in oxygen and incremental doses of thiopentone and fentanyl. The mechanical response of the adductor pollicis to train-of-four stimulation of the ulnar nerve was recorded using the Myograph 2000. A stabilization period of 3 min was achieved before administration of Org 9487, 1.5 mg kg^{-1} (1.5 × ED$_{90}$). Tracheal intubation was performed after 60 s. The anticholinesterase was administered in Groups la and 2a after a further 60 s. Groups lb and 2b received three further doses of Org 9487 0.5 mg kg^{-1} when T1/T0 had recovered to 25%. The anticholinesterase was given 2 min after the third maintenance dose. The recovery times after administration of the anticholinesterase in the four groups were compared using the Mann-Whitney two-tailed *U* test.

The mean (SD) lag time in the 24 patients was 34 (8.0) s, and the mean time to maximum block was 75 (33) s. The mean (SD) time to T1/T0 = 25% in Groups lb and 2b was 17.6 (4.4) min. The mean (SD) recovery times in the four groups after the anticholinesterase are given in table 1.

Rapid antagonism of profound block induced by Org 9487 1.5 mg kg^{-1} cannot be obtained using either neostigmine or edrophonium.

Key words
Neuromuscular block, Org 9487. Pharmacodynamics.

Table 1 Recovery times (SD) (s). (*P<0.05 compared with 1a in same group; †P<0.05 compared with 1b)

	Group 1: Neostigmine		Group 2: Edrophonium	
	a (n=7)	b (n=5)	a (n=5)	b (n=7)
25% T1/T0	8.5 (5.1)	2.8 (0.4)*	6.4 (3.2)	1.0 (0.5)*†
75% T1/T0	19.9 (13.9)	7.2 (1.9)*	18.6 (9.6)	18.0 (12.3)†
T4/T1=0.7	21.8 (9.0)	19.5 (6.3)	23.6 (9.3)	39.0 (7.7)*†
T4/T1=0.8	26.1 (11.2)	24.3 (8.4)	29.5 (13.3)	51.2 (7.6)*†

Acknowledgement

Org 9487 was provided by Organon Teknika plc, who also provided a grant for this study.

Reference

1. Wierda JMK, van den Broek L, Proost JH, Verbaan BW, Hennis PJ. *Anesthesia and Analgesia* 1993; 77: 579–584.

Effect of theophylline and forskolin on human respiratory cilia beat frequency *in vitro*

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Mucociliary clearance represents an important protective mechanism of the upper and lower respiratory tracts. The transport of mucus is dependent on the cilia beat frequency (CBF) and coordination, and the composition of the mucus layer. Previous studies have shown that both theophylline and aminophylline increase mucus transport rate *in vivo*.[1 2] However, the exact site and mechanism of their action are unclear. Both drugs potentiate the cyclic AMP system which could affect both CBF, mucus production or both. We have investigated the effect of theophylline and forskolin (a direct adenylate cyclase activator) on the beat frequency of human respiratory cilia *in vitro*.

CBF was measured using the transmitted light technique in a previously described perfusion system.[3] Nasal turbinates from 15 patients who had undergone turbinectomy for tissue hypertrophy were used as the source of ciliated epithelium. Ciliated discs, 4 mm in diameter, cut from the turbinates were divided into four groups. Group 1 was exposed to theophylline 100 μg ml^{-1} and group 2 exposed to forskolin 100 μg ml^{-1}. Groups 3 and 4 acted as matched controls. The ciliated discs were mounted in paired perfusion chambers at 37°C and connected to a reservoir containing Hanks' balanced salt solution. The samples were perfused for 30 min before a baseline reading of CBF was made (t30). One chamber was then connected to a reservoir containing the drug solution and measurements repeated after 60 min (t90). The investigator was not aware of which chamber received the drug solution.

The results are shown in table 2.

Table 2 Mean cilia beat frequency (SD) (Hz). (**P=0.008 (increased compared with control)

Time (min)	Control	Theophylline	Control	Forskolin
30	12.16 (2.83)	11.02 (3.62)	13.23 (3.23)	11.64 (3.39)
90	11.33 (2.8)	11.58 (3.76)	12.98 (2.72)	14.71 (2.86)**

Nine pairs of ciliated discs were used for the theophylline study. There was no significant change in CBF compared with control. Six pairs of discs were used for the forskolin study. Forskolin 100 μg ml^{-1} significantly increased CBF compared with control.

Key words
Lung, cilia. Model, lung. Theophylline. Forskolin

References

1. Konrad F, Schreiber J, Hahnel J, Kilian J, Georgieff M. *Anaesthetist* 1994; 43: 101–106.
2. Sutton PP, Pavia D, Bateman JRM, Clarke SW. *Chest* 1981; 80: S889–891
3. Selwyn DA, Gyi A, Raphael JH, Key A, Langton JA. *British Journal of Anaesthesia* 1996; 76: 111–115.

Effect of carbon dioxide on cerebral autoregulation as assessed by the transient hyperaemic response test

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We have developed a theoretical model for the quantitative assessment of cerebral autoregulation (CA) using the transient hyperaemic response (THR) seen in the middle cerebral artery (MCA) blood flow velocity (FV) after release of a brief compression of the common carotid artery (CCA).[1] The aim of this study was to use this model to assess the effects of carbon dioxide on CA.

Seven healthy volunteers were studied in the supine position. A continuous record of cerebral blood FV in the left MCA using transcranial Doppler ultrasonography and of end-tidal carbon dioxide ($P\mathrm{E}'_{\mathrm{CO_2}}$) at the mouth was established. Each volunteer was subjected to three left CCA compressions of 10-s duration for the baseline measurements followed by measurements made while breathing via a rebreathing circuit to achieve $P\mathrm{E}'_{\mathrm{CO_2}}$ of approximately 1 kPa and then 2 kPa above baseline, and finally while voluntarily hyperventilating to $P\mathrm{E}'_{\mathrm{CO_2}}$ of approximately 1 kPa and then 2 kPa below baseline. Mean arterial pressure (MAP) was recorded non-invasively before each CCA compression. Time-averaged mean velocities from the maximal FV traces of the following MCA pulse waves were analysed: the pulse wave just preceding compression (F1); the first pulse wave after compression (F2); and the first pulse wave after release of compression (F3). The expected value of F3 was calculated as F3=F1 × MAP/P2 (where P2 stands for arterial pressure in the MCA immediately after compression of CCA, and is estimated as MAP × F2/F1). The ratio of observed F3 to expected F3 was taken as a measure of strength of autoregulation (SA).[1] A total of 97 THR tests were analysed; the correlation between SA and $P\mathrm{E}'_{\mathrm{CO_2}}$ in the pooled data is shown in figure 2.

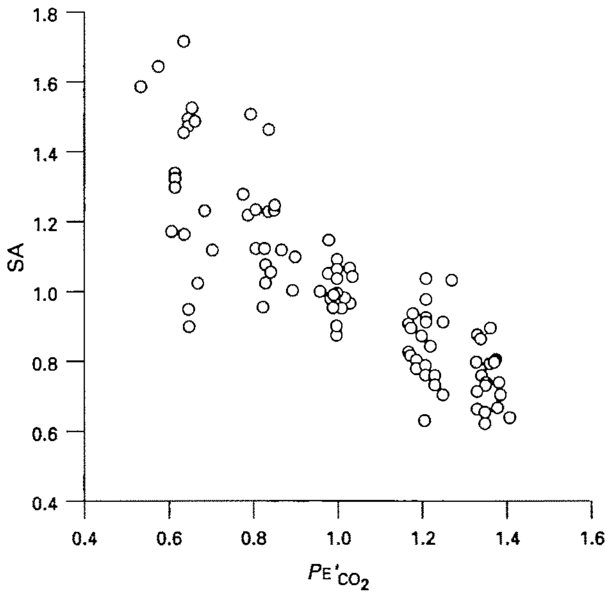

Figure 2 $P\mathrm{E}'_{\mathrm{CO_2}}$ and SA are expressed as multiples of baseline mean for each subject.

Our results demonstrate a significant negative correlation between SA and $P\mathrm{E}'_{\mathrm{CO_2}}$ (r^2=0.72; P<0.001). These findings substantiate previous claims that the autoregulatory response of cerebral vessels is attenuated during hypercapnia. In addition, we have shown that this response can be exaggerated during hypocapnia when assessed by THR test.

Key words
Autonomic nervous system, autoregulation. Brain, blood flow. Gases, non-anaesthetic, carbon dioxide.

Reference

1. Mahajan RP, Macdonald IA. *Journal of Physiology* 1996 (in press).

Comparison of the effect of intrathecal and extradural fentanyl on gastric emptying in labour

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Extradurally administered opioid drugs improve analgesia in labour but have disadvantages such as nausea, vomiting and delayed gastric emptying.[1 2] Intrathecal opioids are becoming popular but their effect on gastric emptying is unknown. This study was designed to assess the effect on gastric emptying of fentanyl given intrathecally, or extradurally in standard clinical doses.

One hundred and five women with uncomplicated pregnancies and in active labour were included in the study with their informed consent and approval of the research Ethics Committee. All had been fasted for at least 3 h and had received no systemic analgesia. Patients were allocated randomly to one of three groups. Group S received fentanyl 25 μg and bupivacaine 2.5 mg intrathecally, Group E 10 ml bupivacaine 0.25% and fentanyl 50 μg extradurally and Group C 10 ml of 0.375% bupivacaine extradurally. A baseline blood sample was taken 15 min later and paracetamol 1.5 g given with 100 ml water.

Blood samples were taken at intervals over the next 3 h and analysed for paracetamol concentrations using the HPLC method. Patients received extradural boluses of 0.25% bupivacaine on request. Pain was assessed using visual analogue scores (VAS). Maximum paracetamol concentration ($C_P$max), and areas under the paracetamol concentration time curve (AUC) at 90 and 120 min were compared using ANOVA. Kruskal–Wallis test was used to compare the time to maximum concentration (tC_Pmax) and VAS. A P value of <0.05 was considered significant.

There were no demographic differences between groups. $C_P$max in Group S was significantly lower than group E, and AUC_{90} and AUC_{120} significantly smaller in S than in groups C and E (table 3). Median (range) tC_Pmax values were 120 (15–180), 82.5 (15–180) and 90 (15–180) min in groups S, E and C respectively ($P<0.05$). These results indicate delayed gastric emptying in the group given intrathecal fentanyl compared with the other two groups. The VAS scores were similar except at 30 min when the scores were significantly lower, reflecting better analgesia, in Group S. Group S also required significantly less bupivacaine.

Table 3 Paracetamol absorption (mean (SD)).(*$P<0.05$ compared with Group E; † $P < 0.05$ compared with Groups C and E)

	Group S	Group E	Group C
$C_P$max (μg ml^{-1})	13.4 (8.82)* (n=34)	17.9 (8.06) (n=34)	15.0 (6.22) (n=33)
AUC_{90} (μg ml^{-1} min^{-1})	430 (491)† (n=34)	736 (504) (n=35)	672 (453) (n=33)
AUC_{120} (μg ml^{-1} min^{-1})	649 (592)† (n=33)	1062 (627) (n=35)	1053 (616) (n=37)

Key words
Analgesia, obstetric. Gastrointestinal tract, emptying. Analgesics opioid, fentanyl. Anaesthetics local, bupivacaine.

References

1. Wright PMC, Allen RW, Moore J, Donnelly JP. *British Journal of Anaesthesia* 1992; **68**: 248–251.
2. Ewah B, Yau K, King M, Reynolds F, Carson RJ, Morgan B. *International Journal of Obstetric Anesthesia* 1993; **2**: 125–128.

Effects of alpha$_2$-adrenoceptor agonists on gastric emptying and gastrointestinal transit in the rat

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Opioids markedly delay both gastric emptying and intestinal transit; however, the effect of alpha$_2$ agonists, adjuncts to anaesthetics, on gastric emptying is unclear. We studied the effect of two such agonists on gastric emptying and gastrointestinal transit in the rat.

Six to 10 male Wistar rats (200–250 g) were used for most doses of each substance. Either clonidine (0.001–1 mg kg^{-1}), dexmedetomidine (0.0001–0.1 mg kg^{-1}: donated by Orion-Farmos Pharmaceuticals), morphine (0.1–30 mg kg^{-1}) or saline was injected i.p. At 30 min radiolabelled saline 1 ml was infused into the stomach. At 1 h, the animal was killed, the gastrointestinal tract was removed and the small intestine was divided into 10 equal segments. The radioactivity in the stomach and each segment of the intestine was counted, and gastric emptying and gastrointestinal transit were calculated. Gastrointestinal transit was assessed using the "geometric centre" (the centre of gravity) (= (CiSi)/ Ci, where Ci = count in segment Si).[1] In another group of rats, either yohimbine, naloxone or saline was injected with an agonist. The Mann-Whitney U test was used for comparison of substances or combinations of substances. The ED_{50} and the 95% confidence limits (CL) were determined using logistic regression of inhibition, with respect to saline, of gastric emptying and of geometric centre on log dose and the Fieller equation in the statistical package GLIM (Generalized Linear Interactive Modelling).

Dexmedetomidine 0.1 mg kg^{-1} caused strong sedation and apparent respiratory depression; therefore, this dose was given in only three rats. Clonidine significantly inhibited gastric emptying ($P = 0.001$) but the inhibitory effect was weak (95% CL for difference from saline: 8.2 and 34.9% at the maximum dose of clonidine, 1 mg kg^{-1}). Dexmedetomidine also significantly but weakly inhibited the emptying ($P < 0.05$; 95% CLs for difference from saline: 3.4 and 15.4% at the next-to-maximum dose, 0.03 mg kg^{-1}). However, both clonidine and dexmedetomidine strongly inhibited gastrointestinal transit (table 4). In contrast, morphine inhibited gastric emptying and gastrointestinal transit to a similar degree. Yohimbine significantly antagonized the inhibitory effects of both clonidine and dexmedetomidine ($P < 0.05$). In contrast, naloxone, which significantly antagonized the effect of morphine ($P < 0.01$), did not antagonize the effect of either of these agonists.

Table 4 ED_{50} (mg kg^{-1}) of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit (with 95% CL). Only lower 95% CL are shown when values are outside the range of doses used

	Gastric emptying	Gastrointestinal transit
Clonidine (n=41)	— (4.6, —)	0.080 (0.049, 0.13)
Dexmedetomidine (n=30)	— (4.3, —)	0.039 (0.027, 0.065)
Morphine (n=52)	2.8 (2.1, 3.8)	1.2 (0.87, 1.7)

Alpha$_2$-adrenoceptor agonists dose-dependently inhibit gastrointestinal transit through the alpha$_2$ adrenoceptor; however, they only weakly inhibit gastric emptying.

Key words
Gastrointestinal tract, gastric emptying. Sympathetic nervous system, alpha$_2$-adrenergic agonists.

Acknowledgement

This study was conducred under animal licences 40/00954 and 40/1397.

Reference

1. Miller MS, Galligan JJ, Burks TF. *Journal of Pharmacological Methods* 1981; 6: 211–217.

Caesarean section; efficacy of morphine patient-controlled anaesthesia *vs* ketorolac infusion

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Patient-controlled analgesia (PCA) with morphine can have disadvantages of drowsiness, dizziness, nausea and vomiting, which are particularly unwanted after Caesarean section. Ketorolac is known to be effective for pain relief especially in combination with opioids.[1] It is usually given by i.m. bolus doses.

Forty-one consenting patients, ASA I or II, presenting for elective Caesarean section under spinal anaesthesia were given ranitidine before operation on the night before and morning of operation. I.v. infusion was commenced and a spinal performed with a dose of 0. 5% heavy bupivacaine as chosen by the anaesthetist. Towards the end of the operation all patients were given 10 mg morphine and 10 mg ketorolac i.v. Each patient was then allocated to one of two groups.

The morphine group received a PCA pump containing morphine 60 mg + cyclizine 100 mg in 60 ml saline. Bolus i.v. doses of 1 mg with a lockout of 5 min were set with no background infusion. Ketorolac 30 mg i.m. 8-hourly was prescribed for escape analgesia.

The ketorolac group received a PCA pump with ketorolac 90 mg in 60 ml. This was run at a rate of 2.55 mg h^{-1}, with bolus dose of 0.15 mg, and lockout of 10 min was used to help blind the study (60 mg over 24 h with 30 mg available for boluses giving a maximum of 90 mg in 24 h). Cyclimorph 10 i.m. 3-hourly was prescribed as escape analgesia. Both groups were prescribed prochlorperazine 12.5 mg 8-hourly.

The pumps were continued until the morning after operation. Routine postoperative observations were made by the midwives, together with pain scores (1=none, 2=mild, 3=moderate, 4=severe), nausea/vomiting (1–4), and sedation (1–4). All patients were reviewed 24 h after operation and asked to give a satisfaction score of 1 (awful) to 5 (excellent) (table 5).

Table 5 Pain and satisfaction scores. (NS=not significant; MW=Mann–Whitney; KW=Kruskall–Wallis)

	Morphine		Ketorolac
Number of patients	21		20
Total pain events 1, 2	208/230	NS	191/218
Total pain events 3, 4	22/230	KW	27/218
Av. drug dose (mg) (range)	49 (24–71)		56 (30–71)
No. of escape doses	4 in 3 pts		10 in 8 pts
Satisfaction score			
3, 4, 5	20/21	NS	17/20
1, 2	1/21	MW	3/20

Nausea and vomiting scores, and sedation scores were surprisingly similar in both groups. The total number of unsatisfactory (score 3 or 4) pain score events was not significantly different between groups, nor were the pain scores significantly different at any time interval postoperatively (Kruskall–Wallis). The final satisfaction score was also not significantly different between the groups.

Patients for Caesarean section have less pain than those for upper abdominal surgery and, in addition, have a positive psychological factor.[2] Consequently the requirement for analgesia is less. We have shown that a ketorolac infusion plus i.m. Cyclimorph for escape analgesia provides comparable pain relief (with less opioid use) with conventional morphine PCA. (We feel that better education regarding the need for adequate escape analgesia could improve the success of the technique.)

Keywords
Surgery, Caesarean section. Analgesics non-opioid, ketorolac.

Acknowledgement

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References

1. Gillies G, Kenny G, Bullingham R, McArdle C. *Anaesthesia* 1987; **42**: 727–731.
2. Ogilvy AJ, Smith G. In: Nimmo WS, Rowbotham DJ, Smith G. *Anaesthesia*, 2nd ed. Oxford: Blackwells, Ch 76: 1570–1601.

Aspirin and the bleeding time

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Aspirin is known to impair primary haemostasis by inhibiting platelet aggregation and thus prolonging the bleeding time. The ingestion of aspirin within 7–10 days is a relative contraindication to the siting of an extradural catheter, unless the bleeding time is shown to be less than 10 min.[1] The prolongation of the bleeding time in response to aspirin is variable, with 15–20 % of the adult population being hyper-responders.[2] The present study was designed to determine how the prolongation of the bleeding time, induced by low dose aspirin, changes over the first 48 h of discontinuing therapy.

Forty-eight adult ASA I volunteers were recruited from the staff of the City Hospital. After informed consent volunteers were entered into the randomized, double-blind, placebo-controlled trial, and received a 7-day course of either once daily low dose aspirin (75 mg or 300 mg), or placebo. A baseline bleeding time was performed on each volunteer before therapy and again 2, 9, 24 and 48 h after the last trial tablet. The main outcome measure was the bleeding time at 48 h (table 6).

Table 6 Mean (SD) bleeding times (s) during the 48 h after stopping aspirin. (BT = bleeding time)

Group	Baseline BT	Peak BT	48-h BT
75 mg	274 (67)	437 (145)	323 (83)
300 mg	229 (57)	479 (301)	313 (127)
Placebo	253 (60)	234 (70)	233 (88)

The mean prolongation of the bleeding time caused by 75 mg and 300 mg of aspirin was 162 and 246 s respectively. In all there were six hyper-responders. Their mean prolongation was 504 s. At 48 h the bleeding times were prolonged by 49 and 64 s respectively in the 75-mg and 300-mg groups. The mean bleeding time for the hyper-responders at this time was 72 s above baseline. In each of these groups the bleeding time at 48 h was significantly different from their respective baseline values ($P<0.05$; paired t-test). However, the bleeding time in all volunteers at 48 h was well below the 10-min limit and, importantly, the time course of effect was similar whatever the dose, and whatever the magnitude of response we saw.

For healthy volunteers, the bleeding time 48 h after stopping a 7-day course of low dose aspirin is within the normal range, and close to their baseline values.

Key words
Analgesics non-opioid, aspirin. Blood, anticoagulants.

References

1. McDonald R. *British Journal of Anaesthesia* 1991; 66: 1–3.
2. Fiore LD, Brophy MT, Lopez A, Janson P, Deykin D. *American Journal of Clinical Pathology* 1990; 94: 292–296.

Pharmacokinetics of atracurium after paediatric orthotopic liver transplantation

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Atracurium besylate is widely used by infusion in adult intensive care practice, but there is little information about its kinetics and safety in paediatric intensive care. This study was conducted in children after orthotopic liver transplantation (OLT), as a suitable model for critically ill children.

Ten children (five male) were studied after OLT on return to the ICU. The mean (range) age was 36 (7–78) months, and weight 6–24.2 kg. One child died in the ICU, and one had chronic renal impairment not requiring dialysis. Atracurium was started in theatre at induction of anaesthesia, and adjusted in the ICU according to clinical need. Neuromuscular block was measured using accelerometry (TOFguard) and TOF ratio or count. Arterial plasma samples for atracurium and metabolites taken before, every 12 h during, and at frequent intervals after, the infusion; were processed and stored using standard methods; and analysed by HPLC. Results are given as means (range).

The mean maximum infusion rate during steady state conditions was 1.44 (0.48–3.13) mg kg^{-1} h^{-1}, and the duration of infusion 36.9 (22.5–98.4) h. Tachyphylaxis was not observed. Atracurium $T_{1/2}$ was 18.8 (12–32.3) min, similar to critically ill adults[1] and paediatric surgical patients. CL_{ss} was 13.9 (7.9–20.3) ml min^{-1} kg^{-1}, and V_D 390 (124–551) ml kg^{-1}, both higher than in adults after successful OLT.[2] Laudanosine Cmax was 1190 (400–1890) ng ml^{-1} and $T_{1/2}$ 3.9 (1.1–6.7) h. Renal clearance was 1.3 (0.1–5.8) ml min^{-1} kg^{-1}, and increased with urine flow, but there was no relationship with serum creatinine. Steady state conditions could not be obtained for calculation of laudanosine CL_{ss}. EEG spikes were identified for one child only; the corresponding laudanosine Cmax was 720 ng ml^{-1}. Monoquaternary alcohol Cmax was 986 (330–1770) ng ml^{-1}, and $T_{1/2}$ 42.9 (30–57.7) h. Mean recovery time to a TOF ratio >0.75 was 23.6 (12–27) min.

Atracurium is an effective and safe neuromuscular blocking agent in this population. Laudanosine clearance is normal given satisfactory graft function.

Key words
Paediatrics. Liver, transplantation. Neuromuscular block, atracurium. Pharmacokinetics.

References

1. Parker CJR, Jones JE, Hunter JM. *British Journal of Anaesthesia* 1988; **61**: 531–540.
2. Bion JF, Bowden MI, Chow B, Honisberger L, Weatherley B. *Intensive Care Medicine* 1993; **19**: S94–98.

Effect of remifentanil on the auditory evoked response and haemodynamic changes after intubation and surgical incision

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The ability of remifentanil to suppress the cortical and autonomic effects of intubation and incision was investigated. We examined the effect of remifentanil in combination with either propofol or isoflurane on the auditory evoked response (AER) and haemodynamic variables. The amplitude of the early cortical AER wave (Pa) has been shown to be a sensitive monitor of depth of anaesthesia,[1] increasing in amplitude following laryngoscopy/intubation[2 3] and surgical incision.

Twelve patients undergoing hernia repair or varicose vein surgery were randomized to receive either an inhaled anaesthetic using isoflurane or a total i.v. technique using propofol. In both cases this was accompanied by an infusion of remifentanil. Anaesthesia was induced with remifentanil 1 μg kg^{-1} and propofol (mean 80 mg). Neuromuscular block was achieved with atracurium (0.6 mg kg^{-1}) before intubation. In both groups the patients' lungs were ventilated with an oxygen/air mixture. Remifentanil was administered as a continuous infusion of 0.5 μg kg^{-1} min^{-1} reducing to 0.25 μg kg^{-1} min^{-1} 5 min after intubation. Propofol was infused at 9 mg kg^{-1} h^{-1} reducing to 6 mg kg^{-1} h^{-1} after 10 min. Isoflurane concentration was maintained at 0.6% end-tidal. The AER, systolic pressure, diastolic pressure and heart rate were measured before and after intubation and incision to determine any changes in the cortical or autonomic response to these stresses.

The effects of intubation and incision on the AER and haemodynamic variables were not statistically significantly different between the remifentanil/propofol or remifentanil/isoflurane group. When the data for the two anaesthetic combinations were pooled the only significant effects were increases in the diastolic pressure and heart rate immediately after intubation (table 7). However, these were no longer seen 5 min after intubation. There were no cardiovascular responses to incision. There were no significant changes in the AER after intubation or incision.

Table 7 Mean (95% CI) of haemodynamic variables (n=12). (*Post *vs* pre-intubation, P=0.035. †Post *vs* pre-intubation, P=0.014)

	SBP (mm Hg)	DBP (mm Hg)	HR (mm Hg)
Pre-intubation	91 (82–100)	49 (43–55)	61 (56–65)
Post-intubation	103 (93–112)	58 (52–64)*	69 (64–73)†
Pre-incision	98 (88–107)	56 (50–62)	60 (55–65)
Post-incision	96 (87–105)	58 (55–65)	62 (57–67)

In previous studies increases in Pa of 36%, 53% and 60% [2 3] were seen after laryngoscopy/intubation. An increase of 29% would be detected at the 5% level of significance (assuming a power of 80%) in this study. These results indicate that the potent opioid remifentanil in combination with either propofol (6 mg kg^{-1} h^{-1}) or isoflurane (0.6% end-tidal conc) can obtund the autonomic and early cortical effects of intubation and incision.

Key words
Analgesics opioid, remifentanil. Anaesthesia, depth.

Acknowledgement

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References

1. Thornton C. European Journal of Anaesthesiology 1991; **8**: 89–107.
2. Richmond CE, Matson A, Thornton C, Dore CJ, Newton DEF. *British Journal of Anaesthesia* 1996; **76**: 446–448.
3. Brunner MD, Nathwani D, Rich PA, Thornton C, Dore CJ, Newton DEF. *British Journal of Anaesthesia* 1996; **76**: 34–37.

Effect of propofol on the electrocorticogram in patients undergoing cortical resection

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It has been claimed that propofol can cause epileptic seizures despite contradictory evidence that it reduces the clinical effect of electroconvulsion therapy in psychiatry[1] and has anticonvulsant properties.[2] The aim of this study was to compare the effects of clinical doses of propofol with thiopentone on epileptiform activity on the electrocorticogram (ECoG) in epileptic patients undergoing cortical resection.

Fifteen patients with longstanding epilepsy were premedicated with papaveretum 0.2–0.3 mg kg^{-1} and hyoscine 0.4–0.6 μg kg^{-1}. Anaesthesia was induced with i.v. thiopentone 3–7 mg kg^{-1}. Neuromuscular block was produced with atracurium 0.5–0.6 mg kg^{-1} and maintained using an infusion of 0.3–0.5 mg kg^{-1} h^{-1}. The lungs were ventilated with 0.5–2% isoflurane in a mixture of 70% nitrous oxide and oxygen. The systolic blood pressure was maintained >100 mm Hg and mean blood pressure >60 mm Hg by adjustment of inspired isoflurane concentration and i.v. fluid administration. End-tidal carbon dioxide was 3.5–4.5 kPa and nasopharyngeal temperature 36.8–37.4°C. The drugs were administered in a crossover fashion before cortical resection; thiopentone 25 mg or propofol 20 mg was given i.v. every 30 s to a maximum of 5 mg kg^{-1} or until burst suppression. The ECoG was recorded throughout the administration and 10 min thereafter. After return of baseline ECoG, the crossover administration was performed. The recordings were assessed by a neuroelectrophysiologist (C.B.).

Activation of the ECoG was defined as either an increase of spike waves from baseline > 3 per 10 s or extension which was defined as the development of spike waves in more than one new site. All ECoG became isoelectric in patients who were given propofol at or below 1 mg kg^{-1}, while thiopentone administration up to 2.5 mg kg^{-1} produced burst suppression (table 8).

Table 8 Effect of propofol and thiopentone on activation and extension of spike waves in EcoG (No. of patients)

	Activation	No activation	Extension	No extension
Propofol	10	5	6	9
Thiopentone	12	3	5	10

Propofol and thiopentone both produced activation and had similar effects on the ECoG regarding topography and type of discharge. Propofol in the dose employed produced burst suppression more rapidly than thiopentone. Propofol did not cause more epileptiform activity than thiopentone did in epileptic patients undergoing cortical resection. Propofol uniformly induced isoelectic ECoG recording at 1 mg kg^{-1} or less, that is a subclinical dose for induction of anaesthesia. Propofol can be used as an alternative to thiopentone for activation of the EcoG before cortical resection, but the bolus doses administered should be smaller than those used in this study.[3]

Key words

Anaesthetics i.v., propofol. Complications, epilepsy.

References

1. Simpson KH, Halsall PJ, Carr CME, Stewart KG. *British Journal of Anaesthesia* 1988; **62**: 343–344.
2. Mackenzie SJ, Kapadia F, Grant IS. *Anaesthesia* 1990; **45**: 1043–1045.
3. Smith M, Smith SJ, Scott CA, Harkness WFJ. *British Journal of Anaesthesia* 1996; **76**: 499–502.

Comparison of the effects of halothane and isoflurane on the electroencephalogram of the horse

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In humans, halothane and isoflurane have both been shown to reduce median (F50) and spectral edge (SE95) frequency of the EEG and to abolish middle latency auditory evoked potentials (MLAEP). Despite these similar effects, most of the changes seen with isoflurane occur at concentrations below MAC, while progressive changes can be seen with halothane at concentrations up to approximately 2 MAC.[1] The EEG effects of these agents in the horse appear to be similar to those in humans,[2] but changes in F50, SE95 and MLAEP have not been directly compared. The aim of this study was to compare the EEG effects of isoflurane and halothane in the horse.

Eight healthy Welsh Mountain ponies weighing between 270 and 325 kg were anaesthetized on two separate occasions using i.v. thiopentone 10 mg kg^{-1} without premedication. At least 2 weeks was allowed between subsequent anaesthetics in the same animal. On one occasion anaesthesia was maintained using halothane in oxygen and on the other isoflurane in oxygen. IPPV was adjusted to keep end-tidal carbon dioxide between 5.3 and 5.9 kPa. Arterial pressure was monitored using a cannula placed in the right carotid artery which had previously been raised to a subcutaneous position. End-tidal anaesthetic agent concentration was monitored using a piezoelectric agent monitor (Kontron agent monitor 7860).

After 60 min of anaesthesia the end-tidal halothane or isoflurane concentrations were adjusted to 0.8% or 1.2% respectively corresponding to just below MAC for each agent. When the end-tidal concentration had been stable for 10 min, 15 min of single channel EEG were recorded using a dedicated preamplifier with a built-in auditory stimulus generator (Alert system, Medelec). F50, SE95 and MLAEP were calculated from the EEG for sequential 1-min epochs. The second differential of the MLAEP (DD) was calculated in order to facilitate comparison. The recording process was repeated for 1.0% and 1.2% halothane and 1.5% and 1.8% isoflurane corresponding to approximately 1.25 and 1.5 MAC. Normocarbia and the absence of hypoxaemia were confirmed from arterial blood gas samples taken at the beginning and end of each recording period.

There was a statistically significant reduction in SE95 at each subsequent end-tidal halothane concentration from 13.9 (2.6) Hz (mean (SD)) at 0.8% to 11.9 (1.1) Hz at 1.2%. In addition, the DD at 1.2% halothane (21 (6.5)) was significantly less than that at 0.8% halothane (27.6 (11.4)). The only statistically significant difference in the isoflurane data was an increase in SE95 from 10.2 (1.5) Hz at 1.5% to 10.8 (1.6) Hz at 1.8%. The value at 1.2% was intermediate. There was a progressive increase in the incidence of burst suppression with increasing isoflurane concentration. No burst suppression was seen during halothane anaesthesia. The values of SE95, F50 and DD seen at all three isoflurane concentrations were similar to those seen at 1.2% halothane.

The EEG effects of halothane and isoflurane appear to occur at different concentrations of these agents in terms of multiples of MAC.

Key words

Monitoring, electroencephalography. Horse. Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane

Acknowledgement

This study was conducted under animal licence 80/666.

References

1. Lloyd-Thomas AR, Cole PV, Prior PF. *British Journal of Anaesthesia* 1990; 65:306–313
2. Auer JA, Amend JF, Garner HE, Hutcheson DP, Salem CA. *Electroencephalographic Responses* 1979; 3: 130–134.

Topographic distribution of the bispectral index

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The bispectral index (BIS) is a single numeric variable derived from a raw EEG signal. It is derived using an algorithm utilizing both linear and non-linear data and can therefore reflect changes in the phase, power and frequency of the EEG. The BIS is dependent upon the depth of anaesthesia and the degree of surgical stimulus. It has been used to predict movement at incision[1] and may be useful to detect awareness. Published studies have used lead arrangements (montages) which include electrodes within the hairline. These inhibit its introduction into clinical practice, but more convenient montages have not been validated and the BIS may be montage dependent.

We have compared a clinically convenient bifrontal montage with a frontocentral montage for security of lead placement, impedance, signal quality and BIS values. Electrodes were placed at F$_7$, Fp$_z$, F$_8$, C$_3$, C$_4$ and mastoid. When F$_7$ and F$_8$ lay inside the hairline, the electrodes were placed slightly medially. Frontal and mastoid sites were degreased with isopropanol, abraded with Nuprep (D.O. Weaver & Co., USA) and paediatric Ag/AgCl self-adhesive ECG electrodes (NiKo Medical Products) applied. The scalp was abraded with NuPrep and silver dome electrodes applied using Ten 20 (D.O.W) adhesive paste. The BIS and a signal quality index (SQI) were computed by an A-1000 EEG (Aspect Medical, USA) from the F$_7$-Fp$_z$ and F$_8$-Fp$_z$ pairs and from the F$_7$-C$_3$ and F$_8$-C$_4$ pairs. Anaesthesia was not controlled.

Data were collected by computer every 15 s. The median SQI for each montage was calculated for each patient. The BIS for the two montages, excluding data associated with SQI<75%, were correlated. A manual note was made when an electrode needed replacement. The electrode impedances were recorded by the computer whenever an impedance check was requested during the case, commonly when resiting an electrode. The last impedance value only from such an episode was used in the analysis.

Results are presented from 10 patients undergoing a variety of surgical procedures. The reliability of electrode replacement is summarized in table 9. The median SQI of the two montages were not significantly different. Excluding periods of poor signal

Table 9 Reliability of electrode placement

Electrode	F$_7$	Fp$_z$	F$_8$	C$_3$	C$_4$
No. of replacements needed	0	4	0	9	11
Median impedance (Ω)	2050	2200	3500	1500	3800

quality, the correlation coefficient between the BIS calculated from the frontal and the frontocentral montages was 0.75.

We conclude that a frontal montage provides a more convenient and secure EEG, but the BIS from the two sites may not be equivalent.

Key words
Monitoring, electroencephalography. Anaesthesia, depth.

Reference

1. Vernon J, Lang E, Sebel P, Manberg P. *Anesthesia and Analgesia* 1995; **80**: 780–785.

Assessment of frequency of audit of pain in day-case surgery

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Pain is a potent cause of patient dissatisfaction and is the single most important factor in the delay in returning to normal activity after day-case surgery.[1] In the USA, many day surgery units routinely contact patients by telephone to assess recovery after discharge.[2] The objective of this study was to determine the incidence of assessment and audit of postoperative pain in day-case patients in the UK.

Fifty schedule one hospitals, from the document "Recognition of hospital posts under the FRCA regulations", were chosen at random. A telephone interview was conducted with a senior registrar or consultant anaesthetist involved with day-case anaesthesia in the selected hospital. It was possible to obtain completed questionnaires from all 50 hospitals.

All the hospitals performed day case surgery, although only 42 (84%) had separate day-care facilities. There was a consultant anaesthetist in charge of day-case anaesthesia in 26 (52%) of the hospitals, although only one of these had no separate day-care facilities.

Some method of assessing pain was used in 32 (64%) of the hospitals before discharge, though the majority of these (17) used an informal, bedside assessment. Of the units which used a formal type of in-hospital assessment, most (12) used a pain score out of 4 or 10. The other units (3) used a visual analogue score (VAS). By contrast, 36 (72%) of the hospitals did not routinely assess postoperative pain after discharge from hospital. Of the minority that did, most (7) phoned the patients at home on the night of surgery, while some (4) asked the patients to fill in a questionnaire and the others (3) had a nurse visit the patients at home.

Of the 50 hospitals, audit of postoperative pain was performed in 20 (40%) of the units before discharge, and in 23 (46%) of the units once the patients had returned home.

Those hospitals with a consultant responsible for day-case anaesthesia were more likely to perform audit, both in-hospital (17) and after discharge (15), than those units with no designated consultant (corresponding figures 3 and 8 respectively).

Audit is the means by which we can assess the incidence of pain after day-case surgery and then close the loop by improving clinical practice in order to reduce the incidence of this complication.

Key words
Pain. Surgery, day-case.

References

1. Fraser RA, Hotz SB, Hurtig JB, Hodges SN, Moher D. *Pain* 1989; **39**: 189–201.
2. Newson CD, Nathanson MH, White PF. In: Healey TEJ, Cohen PJ, eds. *A Practice of Anaesthesia.* London: Edward Arnold, 1995; 1363–1390.

Respiratory depression following morphine and alfentanil in combination

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Patient-controlled analgesia could be improved if rapid onset analgesia followed the bolus administration but with a morphine-like duration of action. The equipotent dose ratio of morphine to alfentanil has been quoted as 10–15:1.[1]

Thirty consenting ASA I and II patients, aged 19–71 presenting for body surface surgery were studied in three groups of 10. All were anaesthetized with propofol, laryngeal mask and spontaneous respiration with isoflurane through a Lack circuit. Fresh gas flow was adequate to ensure there was no rebreathing.

All patients were routinely monitored in addition to end-tidal carbon dioxide (Datex Capnomac Ultima), computed minute volume (CMV) and respiratory rate (Mercury Computing Spirometer CS7) recording onto chart recorders. When stable respiration was established, patients were given an i.v. bolus of morphine 2 mg, alfentanil 0.2 mg or a mixture of both, via a syringe driver over 1 min. Recording was continued for a further 15 min after which anaesthesia was deepened before surgery.

Mean age (55.9, 46.6, 49.6 yr), weight (74.5, 75.1, 83.1 kg), and sex distribution was similar in all groups. After drug administration, there was a slow reduction in CMV in the morphine group which had reached a plateau by the end of the recording, whereas the alfentanil group showed a rapid decrease, maximal at 2 min, thereafter returning towards baseline. The combination group also showed a rapid decrease maximal at 2.5 min, thereafter similar to the morphine group (fig. 3). Mean end-tidal carbon dioxide rose by 4 mm Hg at 12 min, 5 mm Hg at 5 min and 6 mm Hg at 12 min, respectively for the three groups, and respiration rate decreased by 2 bpm at 12 min, 6 bpm at 3 minutes and 7 bpm at 5 min.

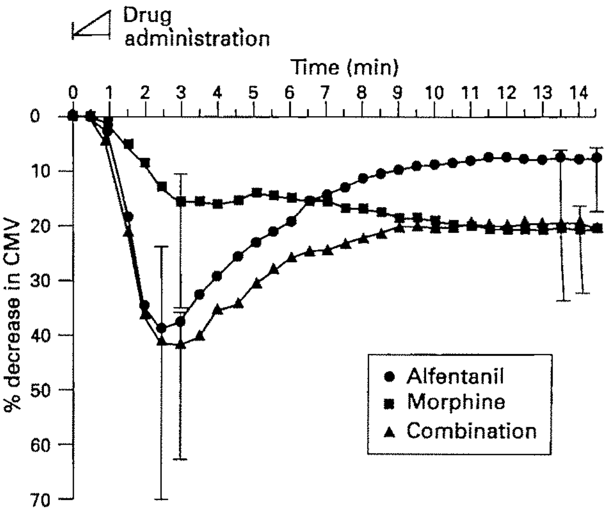

Figure 3 Mean percentage change in computed minute volume (CMV) and range.

Although the maximal carbon dioxide increase in the combination group was higher, the maximal changes in respiration rate and CMV were not markedly greater in the combination group than with alfentanil alone. The delivery of the drugs over 1 min was to simulate patient-controlled analgesia (PCA) administration. Our morphine dose was twice the commonly used PCA bolus to emphasize the respiratory effects. The objective of rapid analgesic effect[2] (implied by respiratory changes) without overshoot would have been better achieved with a lesser alfentanil ratio, although we cannot directly relate our findings to the awake patient.

Key words
Analgesics opioid, alfentanil. Analgesia, patient-controlled.

Acknowledgement

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References

1. Lehmann KA. Advances in Pain Research and Therapy 1991; 18: 481–506.
2. Black TE, Kay B, Healy TEJ. *Anaesthesia* 1984; **39**: 546–548.

Thoracic extradural infusions for pain after thoracotomy: are fentanyl–bupivacaine mixtures better than fentanyl alone?

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Thoracic fentanyl extradural analgesia has been shown to provide better postoperative lung function and shorter hospital stay than i.v. fentanyl and lumbar fentanyl extradural analgesia for patients after thoracotomy.[1] The quality of fentanyl extradural analgesia may be improved by the addition of low dose bupivacaine although the benefits or otherwise of this technique remain unclear.[2 3]

A randomized double-blind clinical trial was conducted on 106 patients scheduled for resection of lung tissue via thoracotomy. Preoperatively, patients had an extradural catheter inserted at the T5–6 or T6–7 intervertebral space and received a test dose of 3 ml 0.5% bupivacaine with 1 in 200 000 adrenaline. All patients received general anaesthesia for their procedures. The study extradural solution contained 0, 0.1 or 0.2% bupivacaine in combination with fentanyl 10 μg ml^{-1}. Intraoperative analgesia was provided by a 5–10-ml bolus of extradural solution delivered before surgical incision followed by an infusion of between 5 and 10 ml h^{-1} according to clinical requirements. Postoperatively, infusion rates were adjusted and boluses given according to analgesic requirements and occurrence of side effects. Analgesic adequacy at rest and during movement was assessed at 2, 4, 8, 16 and 24 h. All patients received continuous invasive haemodynamic monitoring in an HDU environment for up to 24 h with variables archived at 5-min intervals. Any episodes of respiratory depression, nausea, neurological deficit and pruritus were recorded. Analgesic efficacy was assessed using visual analogue scores (VAS), an observer/verbal ranking scale (OVRS) and by the total extradural solution used.

After patient exclusion, 95 sets of data were available for analysis. An analysis of outcome variables was performed for each time point using the Kruskal–Wallis analysis of variance. A P value of <0.1 prompted pairwise exploration using the Wilcoxon rank sum test. There was a difference in the pain scores at the 2-h (first) measurement time only with higher pain scores in the fentanyl alone group (table 10). Otherwise, there were no between-group differences in pain scores or in the total amounts of extradural solution used. There were no between-group differences in the number of episodes of hypotension or in the number of interventions for hypotension. However, the use of intraoperative vasopressor and the incidence of neurological complications were significantly higher in the 0.2% bupivacaine group. We conclude that in the early postoperative period, the addition of bupivacaine 0.1% improves fentanyl thoracic extradural analgesia without increasing the incidence of side effects.

Table 10 P values for differences in pain scores at 2 h (F= fentanyl alone; FB1 = fentanyl and bupivacaine 0.1%; FB2 = fentanyl and bupivacaine 0.2%)

	F *vs* FB1	F *vs* FB2	FB1 *vs* FB
VAS	0.03	0.08	0.6
VAS with cough	0.01	0.02	0.88
OVRS	0.07	0.03	0.55

Key words
Analgesic techniques, extradural. Analgesics opioid, fentanyl.

References

1. Guinard JP, Mavrocordatos MD, Chiolero R, Carpenter RL. *Anesthesiology* 1992; 77: 1108–1115.
2. Badner NH, Komar WE. *Canadian Journal of Anaesthesia* 1992; 39: 330–336.
3. Badner NH, Bandari R, Komar WE. *Canadian Journal of Anaesthesia* 1994; 41: 387–392.

Propofol protects rat hepatocytes against an oxidant stress

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Propofol (2, 6-diisopropylphenol) is an i.v. anaesthetic agent with antioxidant properties.[1] Using rat hepatocyte suspensions we investigated whether pretreatment with propofol protected nucleated cells against an oxidant stress. The oxidant used was AAPH (2,2'-azobis (2-amidinopropane) dihydrochloride). This is a water-soluble free radical generator which produces maximal cell death in rat hepatocytes when used in a 50 mmol litre^{-1} concentration.[2]

Healthy, adult male Sprague-Dawley rats were killed and hepatocyte suspensions (2×10^6 cells ml^{-1}) prepared using the two-step collagenase perfusion technique.[3] The initial percentage of viable hepatocytes was measured using the Trypan blue exclusion test.[3] Hepatocyte suspensions (3 ml) were incubated and oxygenated in a shaking waterbath at 37°C with propofol (5 μg ml^{-1}) plus AAPH (50 mmol litre^{-1}) ($n = 7$), AAPH (50 mmol litre^{-1}) alone or, in a separate experiment, with 10% Intralipid (0.5 μl ml^{-1}) plus AAPH (50 mmol litre^{-1}) ($n = 6$). Each experiment had untreated control suspensions. Viabilities were measured again at 1, 2 and 3 h.

Control cells showed a decrease in viability with time. The addition of AAPH reduced the viability compared with control at all time points ($P<0.0001$). Pretreatment with propofol significantly reduced this effect at 1 h ($P=0.0013$) but no effect was observed with Intralipid pretreatment at any of the time points (fig. 4).

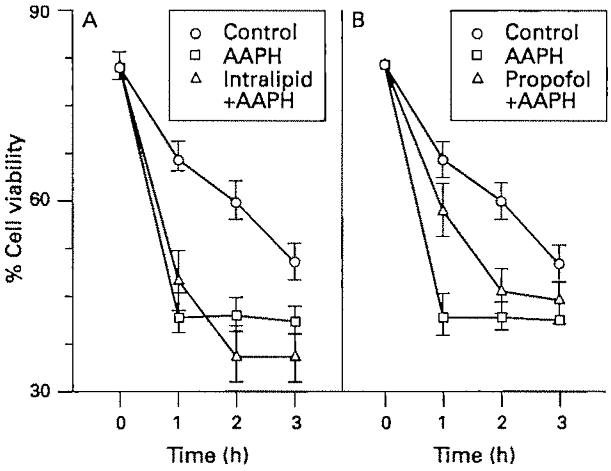

Figure 4 Survival of isolated rat hepatocytes with time in different treatment groups (see text). Bars indicate SEM.

Clinically relevant concentrations of propofol protect rat hepatocytes from an oxidant stress. To our knowledge this has not been demonstrated in nucleated cells before. Propofol may exert its effect in the cell membrane by limiting oxidant mediated lipid peroxidation although other intracellular mechanisms may also be involved.

Key words
Anaesthetics i.v., propofol.

References

1. Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG. *British Journal of Anaesthesia* 1992; 68: 613–618.
2. Matsura T, Yamada K, Kawasaki T. *Biochimica et Biophysica Acta* 1992; 1123: 309–315.
3. Seglen PD. *Methods in Cell Biology* 1976; 13: 29–83.

Effects of post-injury MK-801 on behaviour and neuropeptides in the spinal cord dorsal horn of the mononeuropathic rat

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In the mononeuropathic rat, loose ligation of the sciatic nerve causes loss of the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) in laminae 1–2,[1] and an increase in neuropeptide Y (NPY) in laminae 3–4[2] of the ipsilateral dorsal horn. Only the increase in NPY has been shown to correlate with the hyperalgesia that develops in this model,[2] and pre-emptive administration of MK-801 can delay both the development of hyperalgesia and inhibit the increase in laminae 3–4 NPY.[2] In this study we have investigated the effect of post-injury MK-801, administered after the mechanical hyperalgesia is established, upon behaviour and neuropeptide expression in the spinal cord dorsal horn.

Sciatic nerve ligation or sham operation was performed under isoflurane anaesthesia and animals were allowed to recover for up to 55 days. Animals received MK-801 0.3 mg kg^{-1} (MK group) or equivalent volumes of saline (saline group) by s.c. injection on days 28–34 after operation. Paw withdrawal thresholds to mechanical stimulus were quantified at 14, 35 and 55 day time points, after which the animals were killed and quantitative peptide fluorescent immunohistochemistry was used to analyse the L4–5 spinal cord. Data were analysed by ANOVA with Bonferroni–Dunn correction and are expressed as mean (SEM).

Ligated animals were hyperalgesic when compared with shams at 14 days and hyperalgesia persisted unchanged in the saline group to 55 days. MK-801 reduced hyperalgesia at 35 days (P=0.015), but by 55 days the hyperalgesia scores in MK-801 treated animals were indistinguishable from the saline group.

Ligated animals showed a significant loss (25–35%) of laminae 1–2 SP and CGRP at 35 and 55 days compared with shams. MK-801 had no significant effect upon CGRP at any time point. MK-801 attenuated the loss of SP at 35 days (P=0.048) but had no effect at 55 days. Ligated animals showed ipsilateral increases in laminae 3–4 NPY of 172.3 (24.9)%, 97.1 (11.2)% and 78.3 (8.0)% at 14, 35 and 55 days respectively; these increases were highly significant when compared with equivalent shams. MK-801 treatment attenuated the laminae 3–4 increase in NPY (50.3 (12.9)%) at 35 days when compared with saline group (P=0.03); attenuation was more marked at 55 days (14.4 + 4.4% increase: P<0.0001 *vs* ligated saline group) and laminae 3–4 NPY at this time point did not differ from equivalent MK-group shams.

Therefore, post-injury treatment with MK-801 has only transient effects upon hyperalgesia and neuropeptides SP and CGRP, but has long-lasting effects upon the novel NPY expression in laminae 3–4 of the ipsilateral dorsal horn. While laminae 3–4 NPY correlated with hyperalgesia at 35 days in the MK-group as previously observed with pre-emptive MK-801,[2] no correlation was evident at 55 days after ligation. This suggests that persistent elevation of laminae 3–4 NPY is not essential to the maintenance of pain behaviour in this model of neuropathic pain.

Key words
Pain, neuropathic. Neuropeptides. Rat.

Acknowledgement

This study was conducted under animal licence 80/493.

References

1. Cameron AA, Cliffer KD, Dougherty WD, Willis WD, Carlton SM. *Neuroscience Letters* 1991; 131: 249–252
2. Munglani R, Bond A, Smith G, Harrison SM, Elliot PJ, Birch PJ, Hunt SP. *Pain* 1995; 63: 21–31

Effect of combining tramadol with piroxicam for analgesia after total hip replacement

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Tramadol has been compared favourably with standard opioids for the control of postoperative pain.[1,2] The purpose of this study was to see whether combining the NSAID piroxicam with tramadol for postoperative analgesia after total hip replacement would reduce both the amount of tramadol needed to provide analgesia and the incidence of nausea and vomiting associated with tramadol.

Thirty ASA I–III patients scheduled for total hip replacement were randomized to receive either a 20-mg piroxicam melt (group A) or a placebo (group B) orally preoperatively. Anaesthesia was induced with fentanyl (1–2 $\mu g\ kg^{-1}$) and propofol (1–2 mg kg^{-1}). The airway was controlled with a laryngeal mask for spontaneous ventilation or tracheal tube for controlled ventilation (intubated with 0.5 mg kg^{-1} vecuronium). After induction, the patients received a subarachnoid injection of 12.5 mg of hyperbaric bupivacaine 0.5% at the level of L3–4. Anaesthesia was maintained with a mixture of 60% nitrous oxide and 40% oxygen with 0.1–1.5% isoflurane. In recovery, the patients were connected to a PCA device containing tramadol 500 mg . Pain was assessed hourly using a verbal rating scale (1–5) and the dose of tramadol used was noted. Patients were allowed to receive 10 mg of morphine i.m. if their pain score was 3 or greater. The occurrence of nausea and vomiting and the use of morphine were also recorded.

The groups were comparable for age, sex and weight. Data were analysed using Student's t-test and chi-square analysis. The mean dose of tramadol used by 12 and 18 h was significantly less in group A than group B. The number of patients requiring supplemental morphine and those complaining of nausea and vomiting were also significantly less in group A. Table 11 shows the results.

Table 11 Doses of tramadol (mg) (SEM) used to control pain.(*P < 0.05 compared with group A (Student's t-test); †P < 0.01 compared with group A (chi-square test); ††P < 0.05 compared with group A (chi-square test))

	Group A (n=15)	Group B (n=15)
Mean dose used by 6 h	182.6 (20.07)	203.3 (29.2)
Mean dose used by 12 h	278.5 (22.8)	361.3 (23.2)*
Mean dose used by 18 h	372.3 (30.2)	454.6 (18.7)**
No. requiring supplemental morphine	1	10††
No. complaining of nausea (vomiting)	3 (0)	9 (7)†

Combining tramadol and piroxicam appears to reduce the dose of tramadol needed to provide postoperative analgesia and the incidence of nausea and vomiting.

Key words
Pain, postoperative. Analgesics, tramadol. Analgesics non-opioid, piroxicam. Surgery, total hip replacement.

References

1. Eggers KA, Power I. *British Journal of Anaesthesia* 1995; 74: 247–249.
2. Lehman KA, Jung C, Hoeckle W. *Pain* 1985; 6: 88–100.

POSTER PRESENTATIONS

Ambulatory extradural analgesia in labour reduces risk of Caesarean section

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Extradural analgesia in labour with plain solutions of bupivacaine results in unwanted motor block precluding ambulation. Such extradurals have been associated with an increased incidence of Caesarean section.[1] It has been suggested that maintenance of the upright posture in labour is advantageous.[2] A combined spinal extradural (CSE) technique has been described[3] which delivers acceptable analgesia while maintaining ability to ambulate in labour. We describe preliminary results of work in progress to assess the benefits of maintaining mobility in labour.

Informed consent was obtained from 67 women who were randomly allocated to two groups.

In group 1 a lumbar extradural catheter was sited. A test dose of 50 mg of lignocaine in 2.5 ml was followed by 25 mg bupivacaine in 10 ml. When pain returned further extradural doses of 25 mg of bupivacaine were administered as required

In group 2 a Sprotte spinal needle (24-gauge, 120 mm) was inserted through a 16-gauge Tuohy extradural needle. Bupivacaine 2.5 mg and fentanyl 25 μg were injected into the cerebrospinal fluid. An extradural catheter was then threaded. Extradural doses of 20 μg of fentanyl and 10 mg of bupivacaine in 10 ml were administered when pain returned.

Half hourly pain scores, arterial pressure and mobilization were recorded throughout subsequent labour and delivery. Mode of delivery was recorded at follow up.

The two groups were comparable for age, parity and pain score. No patient in group 1 was able to ambulate whereas all patients in group 2 walked at some time in labour.

There was a significant increase in Caesarean section rate in patients in group 1 (plain bupivacaine group); chi-square test=3.89; $P<0.05$ (table 12).

This study suggests that CSE is associated with a lower risk of Caesarean section than a conventional extradural technique. However, further studies need to be performed to confirm these findings and allow more detailed assessment of the technique.

Table 12 Results. (CSE=combined spinal extradural technique)

Group	Vaginal delivery (spontaneous or instrumental)	Caesarean section
Group 1	26	11
Group 2 (CSE)	27	3

Key words

Anaesthetic techniques, extradural. Pregnancy, labour.

References

1. Thorp JA, Hu DH, Albin RM, McNitt J, Meyer BA, Cohen GR, Yeast JD. *American Journal of Obstetrics and Gynecology* 1993; **169**: 851–858.
2. Nikodem VC. *Cochrane Database of Systemic Reviews* 1993 03334
3. Collis RE, Baxandall ML, Srikantharajah ID, Edge G, Kadim MY, Morgan BM. *International Journal of Obstetric Anaesthesia* 1994; **3**: 75–81.

An explanatory model for postoperative vomiting after gynaecological surgery

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Postoperative nausea and vomiting (PONV) is a common event in gynaecology patients. Identifying in advance those most likely to vomit should allow targeting of treatment to increase safety and effectiveness. We have therefore studied pre- and intraoperative factors potentially predictive of postoperative vomiting.

We have collected data 48 h after operation on patients undergoing major gynaecological surgery. Information was obtained by review of case notes, prescription sheets and direct patient questioning. Postoperative vomiting (PV) and nausea were graded as present or absent; subjective questions regarding severity of symptoms were not asked. A number of potential correlates of outcome were considered: age, weight, preoperative arterial pressure, history of PV, open or laparoscopic procedure, presence of a nasogastric tube, use of nitrous oxide, use of total i.v. (propofol) anaesthesia, maximum change in arterial pressure, intraoperative fluid administration, perioperative antiemetic, administration of ondansetron, duration of surgery, cumulative morphine dose, presence or absence of droperidol added to morphine in the patient-controlled analgesia system (PCAS). Logistic regression analysis was applied to suggest predictors of PV.

We recorded data for 103 patients; 31% (22.1–39.9%, 95% confidence interval) suffered from PV. Nausea was found to be too imprecise and too common an end point (64% (54.7–73.3%)) and so was not analysed further. We suspected an interaction between ondansetron administration and PCAS droperidol; a compound variable was derived (Anaes) which was a significant predictor and improved the accuracy of the model:

Logit (p) = 8.45 (if open surgery) − 8.9724 + 1.8853 (pmh of PV) − 2.2436 (droperidol in PCAS) + 2. 0343 (anaes) − 1. 95 (if NG tube) − 1.59 (if ondansetron)

The overall accuracy of the model was 77.55% ($P<0.0001$)

We have described pre- and intraoperative factors correlating with postoperative vomiting after major gynaecological surgery. Interestingly, antiemetics, nitrous oxide and total dose of morphine seem not to be significant prognostic indicators. These may become significant in a larger data set. In our model the most significant factors in predicting vomiting appeared to be a history of PV and use of droperidol in the PCAS. An odds ratio calculation could be performed for each case according to our equation. Patients could thus be predicted as "will not vomit" or "don't know" (4% (0–9%) *vs* 40% (23–57%) risk of PV), and "high risk" patients targeted with specific antiemetic therapy. A favourable odds ratio would suggest a very low risk of vomiting and so antiemetics could be withheld saving money and avoiding potential drug side-effects.

Key words

Nausea, postoperative. Vomiting. Premedication, ondansetron.

Laryngeal mask airway is associated with reflux in the lithotomy position

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The introduction of the laryngeal mask airway (LMA) to anaesthetic practice has reduced the use of face masks and tracheal tubes. The LMA may increase the incidence of gastro-oesophageal reflux,[2] and lower oesophageal sphincter tone potentiating regurgitation.[2] We investigated both the incidence of regurgitation associated with use of the LMA during general anaesthesia, and whether the LMA protected the larynx if regurgitation occurred.

Hospital Ethics Committee and patient consent were obtained. Twenty patients were included and a standardized anaesthetic technique employed. Two pH electrodes, one in the upper oesophagus, 20 cm from the anterior nares and one passed down the LMA, exiting at the aperture portion of the LMA and being fixed there, were connected to a Digitrapper which continuously recorded pH. A pH drop to <4 was defined as reflux. After induction of anaesthesia the oesophageal electrode was inserted followed by the LMA with electrode. The pH was recorded for the duration of the procedure.

Oesophageal reflux occurred in 12 patients (60%) and the LMA electrode detected reflux in four of these cases. These four patients were in lithotomy position and experienced multiple refluxes (>2). Three further patients were in lithotomy and all experienced oesophageal reflux. Five supine patients refluxed, three being multiple (table 13). No reflux occurred in the first 5 min of monitoring.

Table 13 Reflux characteristics of the supine and lithotomy positions

	No.	Oesophageal reflux	Reflux anterior to LMA	Multiple reflux
Supine	13	5	0	4
Lithotomy	7	7	4	5

Use of the LMA is associated with a high incidence of reflux. Used in the lithotomy position it was found always to cause reflux and in addition refluxed material was found anterior to the LMA in four out of seven patients increasing the risk of aspiration. Regurgitated material passing anterior to the LMA may cause aspiration, and this study suggests there is a risk of aspiration in 20% of cases where the LMA is used.

Keywords

Equipment, laryngeal mask. Complications, regurgitation.

References

1. Owens TM, Robertson P, Twomey C, Doyle M, McDonald N, McShane AJ. *Anaesthesia and Analgesia* 1995; **80**:980–984.
2. Rabey PG, Murphy PJ, Langton JA, Barker P, Rowbotham DJ. *British Journal of Anaesthesia* 1992; **69**:346–348.

Effects of 5-hydroxytryptamine on the partially curarized rat phrenic nerve diaphragm preparation

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5-Hydroxytryptamine has significant effects on the skeletal neuromuscular junction. Previous studies have demonstrated that 5-HT causes facilitatory and depressant effects upon the twitch responses of skeletal muscle in a number of animal models when stimulated at resting rates of stimulation.[1 2] These studies utilized millimolar concentrations of 5-HT. Micromolar concentrations have been shown to facilitate twitch responses after a tetanus, but not at resting rates of stimulation in the indirectly stimulated diaphragm.[3] We decided to evaluate the potential modulatory effects of low concentrations of 5-HT on the rat hemidiaphragm at resting rates of stimulation in a partially curarized preparation.

Phrenic nerve diaphragm preparations were removed from male Wistar rats and suspended in an 18-ml tissue bath containing Krebs Henseleit solution, maintained at a temperature of 37°C and oxygenated with oxygen/carbon dioxide mixture (95%/5%) throughout the experiment. Both hemidiaphragms were pretensioned to 4 *g* resting tension and indirectly stimulated with supramaximal square wave pulses using a 2-ms delay between pulses, a 0.5-ms pulse width and 0.3 Hz rate of stimulation. After an equilibration period, D-tubocurarine was added cumulatively in stepwise increments until all twitch responses were abolished. The concentration which produced 50% block of the twitch response was calculated (EC_{50}). The preparation was exposed to a wash cycle and allowed to re-equilibrate. The EC_{50} of tubocurarine was added to both hemidiaphragms until a stable twitch response was attained (control twitch height). 5-HT was then added in the following concentrations (0, 12.5, 25, 50, 100, 200 and 400 nmol litre^{-1}) allowing the twitch responses to stabilize between each concentration. Equivalent volumes of a control solution (Krebs) were added to the contralateral hemidiaphragm which acted as a time-matched concurrent control. The twitch response to 5-HT was expressed as a ratio over the control twitch height. The ratios were plotted against time and the area under the curve (AUC) calculated. The AUCs for test and control hemidiaphragms were compared by paired *t*-test analysis accepting a 5% significance level. The mean AUC for test (3327 mm^2) and control (4102 mm^2) were significantly different ($P = 0.003$) (fig. 5).

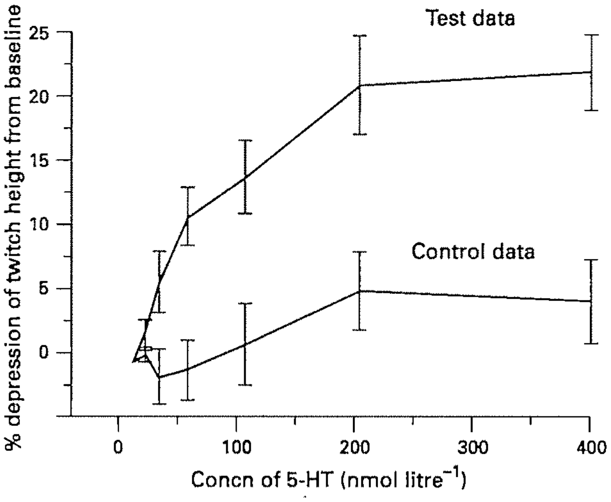

Figure 5 Effects of 5-HT on partially curarized hemidiaphragm. Data points consist of mean and SEM and represent depression in twitch height with increasing concentration of 5- HT (n=7).

We have shown that the addition of low concentrations of 5-HT to the indirectly stimulated rat diaphragm preparation causes a depression in twitch height. This is the first demonstration that 5-HT potentiates the action of curare in an *in vitro* model and gives further evidence of the neuromodulatory role of 5-HT at the neuromuscular junction. Further studies are required to identify the site of action of 5-HT.

Key words
Serotonin, 5-hydroxytryptamine. Rat. Muscle, skeletal, diaphragm.

References

1. Teerapong P, Harvey AL. *Scandinavian Journal of Pharmacology* 1979; 57: 329–334.
2. Dretchen K, Shanheim MM, Lang JP. *European Journal of Pharmacology* 1972; **18**: 121.
3. Hindle AT, Hopkins PM. *British Journal of Anaesthesia* 1994; 74: 483P.

Bispectral index is a state-specific measure of cortical arousal

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The bispectral index (BIS) has been developed by Aspect Medical Systems as a monitor of the hypnotic state of the brain in patients receiving anaesthetic and sedative drugs. BIS has been shown to correlate with responsiveness under sedation and anaesthesia with a variety of agents.[1 2] This study was designed to investigate whether BIS might provide useful information about cortical arousal in other brain states.

We monitored BIS (channels 1 and 2) in three groups of subjects. Group A were patients receiving general anaesthesia for routine surgery (n = 6), Group B were sleeping volunteers (n = 6) and Group C were unsedated subjects recovering from severe head injury (n = 5). Unprocessed EEG was used to confirm sleep. After a period of baseline measurement, we observed the response of BIS to an auditory stimulus, followed by a noxious stimulus (pharyngeal stimulation), in groups A and C. In group B, only the response to an auditory stimulus was monitored. Data were analysed using paired and unpaired Student's *t*-test as appropriate.

The "awake" BIS was lower in group C (46.0 (5.7), mean (SD)) when compared with the other two groups (93.6 (1.5) and 92.8 (1.4) in groups A and B respectively, P <0.01). There was a significant reduction in BIS after induction of anaesthesia in group A ($P < 0.01$) and with the onset of natural sleep in group B ($P < 0.02$). There was no significant difference between the three groups with respect to the minimum BIS (see fig. 6). The BIS in group A, was unaffected by the auditory stimulus and increased minimally after the noxious stimulus. Volunteers in group B were woken by the auditory stimulus with rapid return of BIS to pre-sleep levels. The response to stimulus in group C was inconsistent and set against a background of greater spontaneous baseline variability.

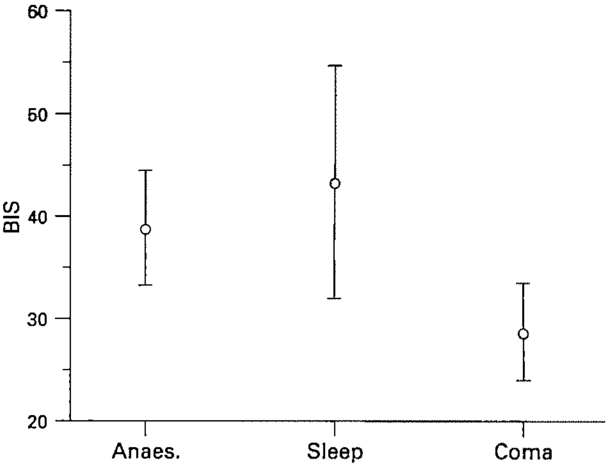

Figure 6 Minimum bispectral index (mean (SD) recorded *vs* group.

Our results demonstrate that a low BIS may occur with sleep, anaesthesia and head injury. While BIS demonstrates potential as a measure of cortical arousal in a variety of brain states, values should only be interpreted with adequate knowledge of the clinical context.

Key words
Brain, electroencephalography.

References

1. Kearse LA, Manberg P, Chamoun N, deBros F, Zaslavsky A. *Anesthesiology* 1994; **81**: 1365–1369.
2. Liu J, Singh H, White P. *Anesthesiology* 1996; **84**: 64–69.

Effects of i.v. anaesthetics and lipid solutions on polymorphonuclear leucocyte chemotaxis *in vitro*

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Anaesthetic agents may impair the chemotaxis of polymorphonuclear cells.[1 2] In the present study we investigated the effects of propofol, thiopentone, methohexitone, midazolam and etomidate in a propylene glycol (Hypnomidate) and a lipid preparation (Etomidat-Lipuro) on *N*-formyl-methionyl-leucylphenylalanine (FMLP)-induced chemotaxis. Additionally, the lipid carriers of propofol (Intralipid 10%) and of Etomidat-Lipuro (Lipofundin-MCT 20%) were tested.

After Ethics Committee approval heparinized peripheral blood was drawn from 30 healthy blood donors. Chemotaxis test was performed as described elsewhere.[3] Briefly, the heparinized blood was mixed with HES (2:1) to enforce sedimentation of erythrocytes. After 30-min incubation the leucocyte-enriched supernatant was harvested and washed twice with phosphate-buffered saline (10 min, 250 *g*, 4°C). The remaining erythrocytes were lysed by using equal volumes of 0.83% ammonium chloride solution. After an additional washing, cells were counted and adjusted to 10^8 ml^{-1} neutrophil granulocytes. For each tested drug 1 ml of the remaining cell suspension was incubated with the respective anaesthetic or 10-fold anaesthetic plasma concentration. Additionally, the Intralipid quantities (0.6 and 6 μl ml^{-1}) which are carrying the anaesthetic and 10-fold anaesthetic propofol concentration and the same quantities of Lipofundin were studied. Random and chemotactic locomotion of the neutrophils in an agarose assay towards a gradient of FMLP (2×10^{-7} mol litre^{-1}) was investigated after a 3-h period of migration. After fixation and staining the migration towards FMLP and in the opposite direction was measured. The difference of the distances was considered to be specific migration. Student's *t*-test was applied for the evaluation of differences.

Specific migration was decreased by thiopentone at both concentrations (400 μg ml^{-1} : 0.13 (0.31); 40 μg ml^{-1}: 1.21 (0.34)) and by propofol at the 10-fold anaesthetic concentration (60 μg ml^{-1} : 1.19 (0.38)). No statistically significant effects on chemotaxis were caused by the other i.v. anaesthetics and the lipid solutions (fig. 7).

These results show that thiobarbiturales in contrast with oxybarbiturates cause a marked concentration-related inhibition of polymorphonuclear cell chemotaxis. The inhibition of migration by propofol in the 10-fold anaesthetic concentration may not be due to its lipid carrier Intralipid whose corresponding concentration had no effect. Also, equivalent quantities of Lipofundin MCT/LCT did not suppress chemotactic migration. Neither the propylene glycol nor the lipid preparation of etomidate influenced polymorphonuclear cell chemotaxis.

Key words
Anaesthetics i.v. Metabolism, lipid. Blood, chemotaxis. Blood, leucocytes.

References

1. Skoutelis A, Lianou P, Papageorgiou E, Kokkinis K, Alexopoulos K, Bassaris H. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 858–862.
2. Jensen AG, Dahlgren C, Eintrei C. *British Journal of Anaesthesia* 1993; **70**: 99–100.
3. Roesler J, Emmendorffer A, Steinmuller C, Luenig B, Wagner H, Lohmann-Matthes ML. *International Journal of Immunopharmacology* 1991; **13**: 931–941.

S-100 concentrations during hypothermic and normothermic cardiopulmonary bypass

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The new assay for β β, and α β units of S-100 (Sangtec 100, Sangtec Medical) is a specific marker of glial cell damage, and is raised in patients with major neurological damage. Cardiopulmonary bypass (CPB) is associated with neuropsychometric damage in up to 80% of patients. CPB used to be performed at hypothermia (32°C), but oxygen saturation in the jugular bulb decreases during rewarming indicating possible cerebral ischaemia. Recently normothermic CPB (37°C) has been proposed to avoid the problems of rewarming, but this removes the known protective effect of hypothermia against brain damage after ischaemia. It is not yet established whether normothermic CPB improves or worsens cerebral outcome compared with hypothermia; serum Sangtec 100 could be useful in assessing the cerebral effects of CPB. We compared the concentrations of S-100 in 15 patients randomized to normothermic (7) and hypothermic (8) CPB. Eight samples were

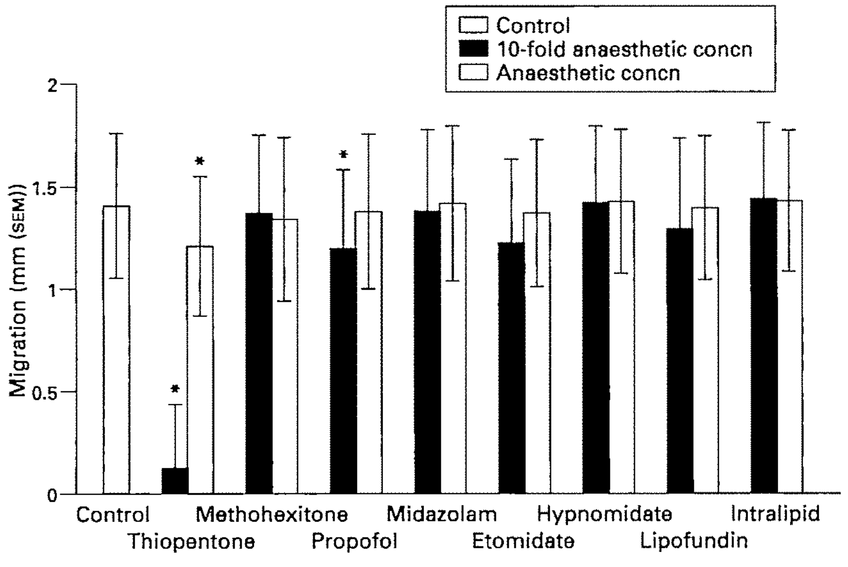

Figure 7 Results expressed as the mean distances (mm (SEM)) covered by polymorphonuclear cells during specific migration in the presence of the tested drugs in comparison with the control. (*P<0.05.)

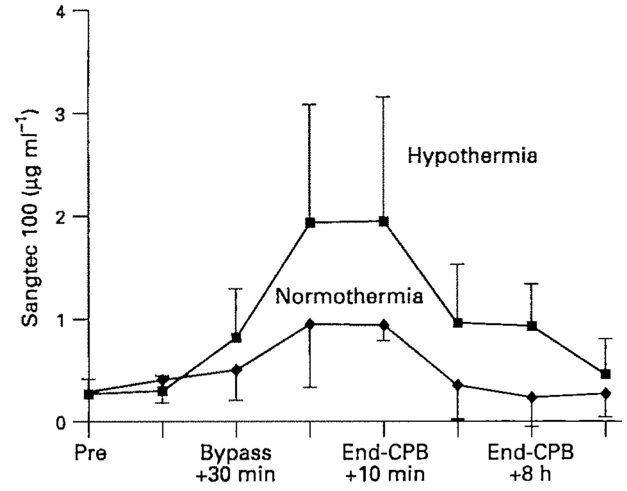

Figure 8 Sangtec 100 concentrations (mean (1 SD)) after cardiac surgery.

collected from the central venous catheter before incision, before bypass, after 30 min CPB, before the end of CPB, 10 min , 60 min and 8 h after CPB, and + 1 day after operation. Samples were spun and the serum frozen for later analysis. Results are shown in figure 8, and statistical comparisons were made by *t*-tests.

S-100 concentrations were increased after rewarming (1.88 µg ml^{-1}, $P = 0.003$) and 10 min after bypass (1.93 µg ml^{-1}), and returned to baseline by 1 day after the operation. Sangtec 100 levels were significantly lower at CPB + 10 min ($P = 0.052$) and returned to baseline 1 h after CPB.

We conclude that CPB produces an increase in S-100 indicating possible mild cerebral damage, but this returns to normal 1 h after the operation. Normothermic bypass produced a smaller increase in S-100 than hypothermic CPB, but we need to establish whether these small, transient increases in S-100 are associated with significant neuropsychometric damage.

Key words

Heart, cardiopulmonary bypass. Nerve, tissue. Protein, S-100. Blood.

Comparative effects of halothane, isoflurane and pentobarbitone on calcium currents in identified molluscan neurons

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Anaesthetics have been shown to depress calcium currents in pedal I cluster neurons of the pond snail *Lymnaea stagnalis*.[1] Here we show the comparative effects of halothane, isoflurane and the barbiturate pentobarbitone on barium currents recorded from identified neurons in the whole brain of *Lymnaea stagnalis* using the two electrode voltage clamp technique.

Snail brains were prepared in snail saline as described previously.[2] The external solution was then switched to one containing the following (mmol litre^{-1}): tetraethylammonium, 30; 4-aminopyridine, 10, Mg^{2+}, 1.5; Cs^{+}, 2; Ba^{2+}, 10; Na^{+}, 6.5; Br^{-}, 30; Cl^{-}, 23; pyruvate, 10; glucose, 5; adjusted to pH 7.8, and allowed to equilibrate for 15 min. Neurons, known as light yellow cells and lying on the ventral surface of the right parietal ganglion, were impaled with two separate microelectrodes filled with (mmol litre^{-1}): KCl, 2500; EGTA (ethyleneglycol- bis(β-amino-ethyl ether) *N*,*N*′-tetra-acetic acid), 500; adenosine triphosphate, 10; titrated to pH 7.7. Tip resistances for both current and voltage electrode were between 8 and 10 MΩ. Inward-going currents were elicited from a holding potential of −70 mV with stepped depolarizations between −50 and + 48 mV in 7-mV steps. Current amplitude was measured at 15 ms (near to the peak) to determine the current voltage relationship. Currents were seen to activate at about −40 mV, reached a peak at −15 mV and then showed only slight deactivation over the pulse duration of 100 ms.

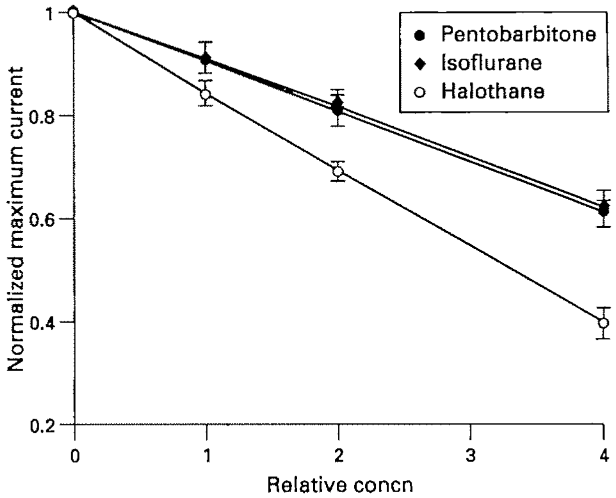

Figure 9 The normalized of peak current amplitudes are plotted against relative drug concentration: Isoflurane and halothane are at 1, 2 and 4% and pentobarbitone at 200, 400 and 800 µmol litre^{-1}. $n = 6$ for halothane. $n = 7$ for isoflurane and $n = 5$ for pentobarbitone.

Figure 9 shows a suppression of peak current both by the anaesthetics and the barbiturate. Linear regressions fitted through each data plot have r^2 values of >0.99, indicating a negative proportional relationship between drug concentration and current and suggesting a possible common pharmacological mechanism. Of the anaesthetics, halothane shows the greatest suppression of current for a given concentration. This mirrors the potency of halothane relative to isoflurane in clinical use.

Key words

Calcium, currents. Model, mollusc. Anaesthetics volatile.

Acknowledgements

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References

1. Yar T, Winlow W. *Journal of Physiology* 1993; 459:12P.
2. Benjamin PR, Winlow W. *Comparative Biochemistry and Physiology* 1981; 70A: 293–307.

British Journal of Anaesthesia 1996; **77**: 697–701

CORRESPONDENCE

Volumetric analysis of aeration in the lungs during general anaesthesia

Sir,—I read with interest the article by Reber and colleagues on volumetric analysis of aeration in the lungs during general anaesthesia.[1] This is a study of radiographic density of the lung, using data consisting of picture elements (pixels) sized 0.9 × 0.9 × 4 mm. The density of the tissue in the pixel varies with the amount of air it contains, and the authors interpret these changes in two ways.

First, they use density to assess the degree of expansion of the lung tissue in terms of aeration. Second, they use changes in density during the breathing cycle to estimate regional ventilation. I would agree that the less dense the lung, the better aerated it is likely to be, because air causes less attenuation than lung tissue (or blood, which here seems to have been assumed to remain a constant fraction of the tissue). Air causes attenuation, in the scale used, of −1000 units, whereas collapsed atelectatic lung causes a much greater attenuation of −100 to +100 units. The authors argue that the distribution of pixel density indicates the distribution of poorly aerated and atelectatic lung. They suggest that the amount of lung tissue in an atelectatic area is four to five times greater than in a normally expanded part of the lung. This implies that by expansion with four times that volume of air, one atelectatic pixel would become five pixels with a normal radiographic density, as the radiographic density of air is very small compared with that of lung tissue. We are left uncertain as to how much air needs to be added to "poorly expanded" lung tissue to convert it into tissue with "reduced aeration" or "normal aeration", although these quantities would be useful for relating the current measures to previous data obtained with other methods.

This knowledge is of particular importance when it comes to drawing conclusions on "distribution of ventilation", as the authors have done in their subjects both during spontaneous breathing and mechanical ventilation. Here it is useful to remember how earlier studies of regional ventilation were performed, as this may help to elucidate some of the findings in the study of Reber and co-workers. Regional ventilation, measured with radioactive xenon, is usually expressed as ventilation in proportion to the volume of that region at total lung capacity (TLC);[2] this is done because at TLC the alveoli are nearly equal in size throughout the lung, and therefore expression of regional volumes and regional ventilation as a proportion of volume at TLC becomes equivalent to expressing these values in terms of "per alveolus". This is more useful than expressing ventilation or lung volume in terms of lung tissue at other states of inflation. If inflation of each part is unequal, then the amount of lung tissue present in each unit volume (in the present case, pixel volume) depends on the amount of distension of the lung that is being considered. Indeed, it is intuitively obvious that erroneous conclusions could result if regional ventilation were based on any other lung volume than the volume at TLC. Consider 100 ml of collapsed lung tissue which is distended by 100 ml of air. It would then have a volume of 200 ml, and if its regional ventilation were expressed as a percentage of the original tissue volume, it would have received 100% ventilation. However, this volume of atelectatic tissue can probably be fully expanded to a volume of approximately 1000 ml and hence if regional ventilation is expressed as a proportion of the volume of tissue at TLC, this ventilation would be 10%. There may be an analogous effect, of an inappropriate denominator, when radiographic density is used as a measure of aeration. This may explain some of the results when Reber and co-workers have "assumed a gas distribution in proportion to the attenuation changes" that they observed between inspiration and expiration. There may be a relationship but it is most unlikely to be a direct linear proportion between density change and regional ventilation.

They report that the radiographic density of the gravitationally upper parts of the lung is less than the density of the lower parts, in subjects at functional residual capacity. Setting aside the distinct possibility that the gradient could also be affected by a gravitationally determined gradient of pulmonary capillary distension, this observation would be expected from many previous measurements made with the isotope technique (for a succinct review, see Milic-Emili[2]). This gradient of density means that the lower pixels contain more alveoli than the upper ones. The article also reports that the lower pixels show a greater change in radiographic density than the upper ones, with a tidal volume inspiration. From an assumption that gas distribution is proportional to attenuation, the authors concluded that "distribution of ventilation" to the dependent regions is two times greater than that to the upper regions. I think that this conclusion is likely to be incorrect. First, as argued above, a change in density from −780 to −840 (approximate changes in the topmost slice) could well represent just as much, or even more, air/alveolus, as a change in density from −570 to −720. The proportional change could perhaps be better expressed as the change relative to the density difference from fully distended lung (say −900 units). If this were considered, then the topmost density change would be from (−900) − (−780) at FRC to (−900) − (−840) at end-inspiration. This gives a fractional change of density of (−60)/(−120) in the topmost level and (−180)/(−330) for the lowest level, and would lead to the conclusion that ventilation was relatively equal from top to bottom. However, this argument depends on the density value taken to represent fully distended tissue and ignores blood contribution to density.

Second, the inference of a vertically uniform distribution of ventilation agrees with findings in subjects breathing spontaneously with normal inspiratory flow rates, where the vertical distribution of ventilation in the lung depends not only on regional compliance but also on differences in airway resistance.[3] [4] A vertical discrepancy in ventilation distribution, such as Reber and colleagues conclude from their data, is only found in sitting subjects in very artificial circumstances when slow manoeuvres are undertaken so that airway resistance differences are minimized. Reber and co-workers did not report tidal volumes, inspiratory duration or ventilatory frequencies of their subjects so the mean inspiratory flow rates cannot be estimated, although these are clearly relevant.

A similar argument should probably be applied to the data obtained in subjects undergoing artificial ventilation which would result in the conclusion that ventilation is distributed preferentially to the upper regions. However, comparison of the data in subjects breathing spontaneously with those whose lungs were ventilated artificially indicates a further difficulty in the use of radiographic density to indicate aeration alone. The tidal volumes of the patients breathing spontaneously are unlikely to have been greater than those of the patients undergoing ventilation with volumes of 8 ml kg^{-1}. What is remarkable is that the change in mean lung density caused by mechanical ventilation (54 units) was smaller than the density change during spontaneous breathing (131 units), although tidal volume was probably less with spontaneous breathing. A factor that could explain this difference is a change in the volume of blood in the lungs during the 10-s breath-hold at end-inspiration necessary for the scan. This change in blood volume in the tissue may well not be uniform from the top to the bottom of the lung. This underlines the fact that factors other than ventilation can affect radiographic density, and this could affect the comparison of measurements made during spontaneous breathing with those made during mechanical ventilation.

Until these questions and uncertainties regarding the proportional relationship of radiographic density and aeration are addressed, I suggest that the inferences from CT studies should be limited to qualitative assessment of aeration, and that the expression "ventilation distribution" is not used.

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1. Reber A, Engberg G, Sporre B, Kviele L, Rothen H-U, Wegenius G, Nylund U, Hedenstierna G. Volumetric analysis of aeration in the lungs during general anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 760–766.
2. Milic-Emili J. Topographical inequality of ventilation. In: Crystal KG, ed. *The Lung: Scientific Foundations.* New York: Raven Press, 1991; 1043–1051.

3. Bake B, Wood L, Murphy B, Macklem PI, Milic-Emili J. Effect of inspiratory flow rate on regional distribution of inspired gas. *Journal of Applied Physiology* 1974; 37: 8–17.
4. Grant BJB, Jones HA, Hughes JMB. Sequence of regional filling during a tidal breath in man. *Journal of Applied Physiology* 1974; 37: 158–165.

Sir,—In his letter, Dr Drummond discusses some important aspects of the measurement of ventilation distribution. We agree that the calculation of ventilation "per alveolus" offers the advantage of taking into consideration the increasing amount of lung tissue, and thus of alveoli, down the lung.

One approach for depicting ventilation per alveolus is to calculate the gas/tissue ratio of a pixel, assuming that the amount of tissue in a pixel reflects the number, or size, of alveoli. In this approach, it can be seen that the difference in ventilation per alveolus of upper and lower lung regions is smaller than per pixel. Using a somewhat different approach, Dr Drummond has also shown this difference and he also pointed out that a shift of blood, either within the lung or in and out of the lung during the breathing cycle, further complicates the analysis. We thus agree with Dr Drummond on these aspects of ventilation calculations. However, relating ventilation to each alveolus is only one way of presenting the results. Ventilation can also be related to the topography of the lung and, for example, to the distribution of atelectasis. In a ventilation–perfusion scan for assessing pulmonary emboli, ventilation is related to pixels, or volume elements, as is the case in our study. These considerations taken together prompted us to present data that have been minimally manipulated.

The amount of gas within a particular pixel of a CT scan can be estimated from the attenuation value of that pixel. This implies that what is not gas is tissue with a certain attenuation value, therefore the measured attenuation is the weighted mean of gas and tissue. In our study, we used the standard scale of Hounsfield units where air has the value of −1000 Hounsfield units (HU) and water 0 HU. We have considered that lung tissue corresponds to water, an assumption that is used frequently for analysis of a CT scan. The changes in attenuation value can be measured in a particular pixel or in a region made up by a number of pixels. Therefore, the change in its gas content can be calculated, which correlates to ventilation. This is what we have done. Our data are consistent with those of Rehder, Sessler and Rodarte who used an isotope technique in awake and subsequently anaesthetized subjects.[1] Even though we agree with Dr Drummond that calculations can be made differently, we consider our conclusion, that ventilation distribution is affected by anaesthesia and mechanical ventilation, with an increase in ventilation to non-dependent regions, is correct.

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1. Rehder K, Sessler AD, Rodarte JR. Regional intra-pulmonary gas distribution in awake and anesthetized–paralyzed man. *Journal of Applied Physiology* 1977; 42: 391-402.

Failed intubation during obstetric anaesthesia

Sir,—Hawthrone and colleagues reported an increase in the incidence of failed tracheal intubation, during Caesarean section under general anaesthesia in their unit, from 1 in 300 in 1984 to 1 in 250 in 1994.[1] As no national data are available they asked if this reflected a national trend. Since mid-1986, data on obstetric anaesthesia have been collected by hospitals in the South West Thames Region. We too have seen a decrease in the use of general anaesthesia for Caesarean section from 66.1% (range 39.8–81.9%) in 1987 to 22.9% (8.8–37.5%) in 1995. The number of general anaesthetics for Caesarean section decreased from 2198 in 1987 to 1320 in 1995. There has been a progressive increase in the incidence of failed intubation, to 1 in 173 in 1994 and 1 in 165 in 1995. Last year in the six units which performed less than 100 Caesarean sections under general anaesthesia, the incidence of failed intubation was 1 in 130; in the seven units that performed more than 100, the incidence was 1 in 188.

Our experience in South West Thames suggests that it is likely that there has been an increase nationally in the incidence of failed tracheal intubation during Caesarean section under general anaesthesia and that one probable cause is anaesthetists' decreased exposure to obstetric general anaesthesia. In the recently published Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–1993, all direct deaths associated with anaesthesia for Caesarean section involved the use of general anaesthesia.[2] Any increase in the incidence of failed tracheal intubation during Caesarean section under general anaesthesia should be a cause for great concern.

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1. Hawthorne L, Wilson R, Lyons G, Dresner M. Failed intubation revisited: 17-yr experience in a teaching maternity unit. *British Journal of Anaesthesia* 1996; 76: 680–684.
2. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–1993.* London: HMSO, 1996.

The intensive care unit cost of surviving and dying

Sir,—The recent editorial by Bion and Strunin[1] introducing the issue on multiple organ failure stated that it costs twice as much to die in an intensive care unit as it does to survive, quoting a reference from 1986.[2] This is true when examining costs of all patients admitted to intensive care. In 1995 our intensive care unit cost was an average of £1997 to manage a patient who survived to leave our hospital, but more than twice this at £4116 to treat a patient who eventually died. The median APACHE II score for these patients was 15 (range 1–48).

When analysis of patient sub-groups is undertaken, however, a different picture emerges. We looked at the costs of treating a group of our most critically ill patients, namely patients referred from the specialties of renal medicine and renal transplant. In this sub-group (median APACHE II score 27 (range 14–48)) the costs, during the same period, of treating those who survived and those who went on to die were similar (£4225 and £4708, respectively).

Thus, the quoted 2:1 ratio in cost of treating survivors and non-survivors may be misleading as the overall cost of a survivor depends on the relatively larger number of less ill patients managed in intensive care who have a good chance of survival.

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1. Bion J, Strunin L. Multiple organ failure: from basic science to prevention. *British Journal of Anaesthesia* 1996; 77: 1–2.
2. Sage WM, Rosenthal MH, Silverman JF. Is intensive care worth it? An assessment of input and outcome for the critically ill. *Critical Care Medicine* 1986; 14: 777–782.

Sir,—We are happy that Drs Thompson and Spiers agree that overall it costs at least twice as much to generate a non-survivor as it does a survivor from intensive care. For example, a 14-month study of 3600 ICU patients at Guy's Hospital showed that 15% of that population died, consuming 37% of the ICU budget in the process.[1] Of course, sub-group analysis generates exceptions to this rule, and in the article[2] which we quoted in our editorial, the authors showed this for patients undergoing elective surgery. These variations are of interest, but they do not alter our main theme, that death in intensive care is doubly wasteful of both lives and resources. It makes sense, therefore, to concentrate on prevention of multiple organ failure which was one of the main themes of the July postgraduate issue of the journal.

J. BION
Intensive Care Society
L. STRUNIN
Postgraduate Editor
British Journal of Anaesthesia

1. Atkinson S, Bihari D, Smithies M, Daly K. Identification of futility of intensive care. *Lancet* 1994; 334: 1206–1266.
2. Sage WM, Rosenthal MH, Silverman JF. Is intensive care worth it? An assessment of input and outcome for the critically ill. *Critical Care Medicine* 1986; 14: 777–782.

Aortic stent surgery

Sir,—We wish to comment on two points made in the letter of Baranowski and Adiseshiah on aortic stent surgery.[1] They noted, and appeared to accept, a mortality of 10% and put forward as a benefit of the stent procedure the fact that "the patient's trachea can usually be extubated early....".

Our own published experience of conventional elective abdominal aortic surgery using a combined general–extradural anaesthetic technique is that hospital mortality is well below 5%, with the trachea of virtually all patients being extubated immediately after surgery.[2] We believe that most centres consider a mortality rate of more than 5% unacceptable, and we support the view of Thompson and Greiff that the stent technique should be introduced with great caution.[3] In addition, fully informed consent must be obtained for all new procedures, even if they are offered to patients in whom the standard technique is considered high risk. Until the rate of conversion to an open procedure (current 35%) is reduced significantly, the stent operation should not be offered to patients who are not considered fit for conventional surgery.

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1. Baranowski AP, Adiseshiah M. Aortic stent surgery. *British Journal of Anaesthesia* 1996; 76: 882–883.
2. Mutirangura P, Stonebridge PA, Clason AK, McClure JH, Wildsmith JAW, Nolan B, Ruckley CV, Jenkins AM. 10-year review of non-ruptured aortic aneurysms. *British Journal of Surgery* 1989; 76: 1251–1254.
3. Thompson MM, Greiff J. Aortic stent surgery. *British Journal of Anaesthesia* 1996; 76: 883.

Sir,—We agree fully with the comments of Wildsmith and McClure that a mortality rate of 10% is unacceptable and that is why we felt moved to write our letter on reading the first publication by Greiff, Thompson and Langham.[1] In that original report they did not indicate clearly the risks. We also agree that patients should give fully informed consent. It is for that reason that the consent in our hospital is obtained by consultant staff.

A recent audit of our mortality rates for open elective surgery using general–extradural anaesthetic techniques and early extubation indicated our mortality to be approximately 1%. We feel that it is inappropriate to increase the mortality risk in these patients by subjecting them to a stent procedure with a 35% conversion rate and 10% mortality risk. However, in common with many centres, we receive referrals where the local team has not been prepared to undertake an open operation as the surgical risks have been considered too great. In these patients we feel that there is an advantage to the closed technique with the mortality probably being less than that after the open approach in this specific group. We have had several such patients only spending a night on the high dependency unit as opposed to the predicted several days. A controlled study examining different techniques and risk groups needs to be carried out.

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1. Greiff JMC, Thompson MM, Langham BT. Anaesthetic implications of aortic stent surgery. *British Journal of Anaesthesia* 1995; 75: 779–781.

A complication of intra-arterial shunting during carotid endarterectomy

Sir,—A 68-yr old male ex-smoker presented after one episode of *amarosis fugax* affecting his right eye and lasting a few minutes. Resolution was complete and there was no residual neurological deficit. Doppler studies showed a 75% luminal obstruction in the right internal carotid and 65% in the left, and he was scheduled for right carotid endarterectomy.

In the anaesthetic room, a Floswitch 20-gauge (Ohmeda) arterial cannula was inserted in the right radial artery, after failed cannulation of the left, for continuous monitoring of arterial pressure. A typical arterial pressure trace was displayed on the monitor. General anaesthesia was induced with fentanyl, etomidate and atracurium, and maintained with isoflurane and 70% nitrous oxide in oxygen.

When dissection of the carotid artery was complete, arteriotomy was performed and a Pruitt balloon shunt inserted. Immediately, the arterial pressure trace became attenuated and the reading changed from 130/70 to 75/65 mm Hg. Flushing the cannula had no effect and free aspiration of blood was possible. Withdrawing the shunt restored a normal arterial pressure trace. It was concluded that the caudal end of the shunt was lying at the junction of the innominate and subclavian arteries and causing significant obstruction to flow of the latter (see fig. 1).

In addition to making the arterial pressure reading unreliable, this could have had a significant impact on cerebral blood flow because the right vertebral artery is a branch of the subclavian. During carotid endarterectomy this further reduction in circle of Willis supply may be crucial. On the left, the subclavian and common carotid arteries have separate aortic origins, and vertebral artery blood flow could not be compromised in a similar manner.

We suggest that the right radial pulse or pressure should be monitored when a right carotid shunt is placed, so that subclavian occlusion can be detected.

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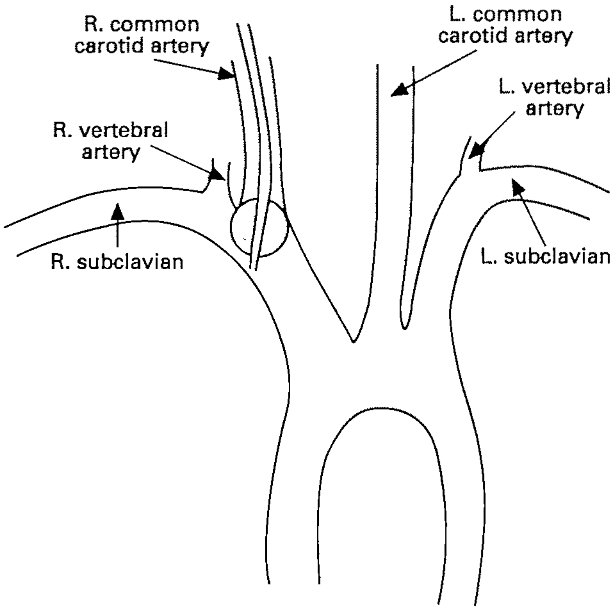

Figure 1 Diagrammatic illustration of the obstruction to flow of the subclavian artery as the caudal end of the shunt was lying at the junction of the innominate and subclavian arteries.

Transoesophageal echocardiography in anaesthesia and intensive care

Sir,—The delay in appearance of an editorial on transoesophageal echocardiography (TOE) in British anaesthesia literature[1] reflects the slow uptake of this tool by British anaesthetists compared with our colleagues on the continent or across the Atlantic.

TOE represents a large initial cost forcing consideration of its benefits, especially in our health system where its use does not allow immediate remuneration (as in the USA). The plethora of uses and undefined benefits to outcome has generated an impression of an expensive toy for the boys. It is now clear that its use can be largely subgrouped into a monitoring role or a diagnostic role. As anaesthetists we have concentrated initially on its monitoring role, especially in relation to regional wall motion abnormalities signifying ischaemia. Unfortunately, the "dancing doughnut", as the short axis monitoring view has been derogatorily termed, has not added significantly to other monitors available and certainly in non-cardiac surgery has not justified its expense. It is not known if the addition of colour kinesis will significantly improve its usefulness. Although many variables may be derived from Doppler data, including cardiac output and left atrial pressures, calculation is usually too cumbersome to allow routine use. However, for the first time TOE allows us to directly assess the volume status of the left ventricle[2] compared with previous indirect estimates of LV filling from pressure data. In addition, with concomitant pressure data TOE can also provide a load-independent measure of contractility.[3]

In contrast, its diagnostic role is now well established in cardiology. That this can translate to the operating room, intensive care or emergency room has now been well documented. In intensive care[4 5] and the emergency room,[6 7] TOE represents a portable easily accessible diagnostic tool. In the operating room we should differentiate between cardiothoracic surgery and other types of surgery. Despite its potential the routine use of TOE in non-cardiothoracic surgery has not been justified except possibly as a volume monitor where extensive blood loss is expected or in the diagnosis of hypotension. In cardiothoracic surgery the diagnostic role of TOE has come into its own. While its monitoring role in routine coronary artery surgery is debatable, its diagnostic role in complex valve,[8] paediatric cardiothoracic surgery[9] and artificial device implantation[10] can contribute significantly to surgical success. In addition, scanning of the aorta for atheroma plaques[11] and left ventricle for residual air pockets[12] has proved useful. After operation, its use can quickly differentiate between the main causes of hypotension and is invaluable in assessing postoperative deterioration.[13]

This diagnostic role in the intraoperative period is having a real impact on the work of cardiac anaesthetists.[14] For the first time the results of a surgical technique are being reviewed by anaesthetists and subsequent decisions based on them, including the need to go back on bypass and modify the surgery. Where these decisions are to be made, there is no doubt that the level of competence is hard to maintain for the occasional cardiac anaesthetist, who may lack credibility in dealing with surgeons and physicians who spend their time solely in a cardiac centre. This may drive us towards dedicated full-time cardiac anaesthetists, at least where complex procedures are undertaken. Indeed, some centres in the USA do not appoint cardiac anaesthetists unless they are competent in TOE.

Why then has the uptake of TOE been so slow to date in the UK? First, the enormous initial capital expense has been difficult to access. Second, there remains a fear of technological obsolescence, with many developments in the pipeline, including colour kinesis, three-dimensional reconstruction and real-time, three-dimensional views. In fact, in the 5 yr since the first editorial quoted by Townend and Hutton,[1] technology has moved from single plane probes to Doppler capability, biplane probes and now multiplane probes with automatic border detection capabilities. Third, an investment of time and training is required before competence is acquired and quality assurance is acceptable. Fourth, its role has not been defined. To these ends, the Society of Cardiovascular Anesthesiologists and American Society of Anesthesiologists have recently published guidelines[15] on perioperative TOE training and use.

In summary, the impact of intraoperative TOE on non-cardiothoracic surgery is yet to be defined. In cardiothoracic anaesthesia, its use is here to stay.

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1. Townend JN, Hutton P. Transoesophageal echocardiography in anaesthesia and intensive care. *British Journal of Anaesthesia* 1996; 77: 137–139.
2. Stoddard MF, Keedy DL, Longaker RA. Two-dimensional transesophageal echocardiographic characterisation of ventricular filling in real time by acoustic quantification: comparison with pulsed Doppler echocardiography. *Journal of the American Society of Echocardiography* 1994; 7: 116–131.
3. Gorcsan J III, Denault A, Gasior TA, Mandarino WA, Kancel MJ, Deneault LG, Hattler BG, Pinsky MR. Rapid estimation of left ventricular contractility from end-systolic relations by echocardiographic automated border detection and femoral arterial pressure. *Anesthesiology* 1994; **81**: 553–562.
4. Khoury AF, Afridi I, Quinones MA, Zoghbi WA. Transesophageal echocardiography in critically ill patients: feasibility, safety, and impact on management. *American Heart Journal* 1994; **127**: 1363–1371.
5. Chenzbraun A, Pinto FJ, Schnittger I. Transesophageal echocardiography in the intensive care unit: impact on diagnosis and decision-making. *Clinical Cardiology* 1994; **17**: 438–444.
6. Saletta S, Lederman E, Fein S, Singh A, Kuehler DH, Fortune JB. Transesophageal echocardiography for the initial evaluation of the widened mediastinum in trauma patients. *Journal of Trauma* 1995; **39**: 137–141.
7. Banning AP, Masani ND, Ikram S, Fraser AG, Hall RJ. Transoesophageal echocardiography as the sole diagnostic investigation in patients with suspected thoracic aortic dissection. *British Heart Journal* 1994; **72**: 461–465.
8. Sheikh KH, de Bruijn NP, Rankin JS, Clements FM, Stanley T, Wolfe WG, Kisslo J. The utility of transesophageal echocardiography and Doppler color flow imaging in patients undergoing cardiac valve surgery. *Journal of the American College of Cardiology* 1990; **15**: 363–372.
9. Ungerleider RM, Kisslo JA, Greeley WJ, Li JS, Kanter RJ, Kern FH, Schulman SR, Nesmith JW, Gaynor JW, Bengur AR. Intraoperative echocardiography during congenital heart operations: experience from 1,000 cases. *Annals of Thoracic Surgery* 1995; **60** (Suppl.).
10. George SJ, Black JJM, Boscoe MJ. Intraoperative transoesophageal echocardiography for implantation of a pulsatile left ventricular assist device. *British Journal of Anaesthesia* 1995; **75**: 794–791.
11. Konstadt SN, Reich DL, Kahn R, Viggiani RF. Transesophageal echocardiography can be used to screen for ascending aortic atherosclerosis. *Anesthesia and Analgesia* 1995; **81**: 225–228.
12. Tingleff J, Joyce FS, Pettersson G. Intraoperative echocardiographic study of air embolism during cardiac operations. *Annals of Thoracic Surgery* 1995; **60**: 673–677.
13. Sohn DW, Shin GJ, Oh JK, Tajik AJ, Click RL, Miller FA jr, Seward JB. Role of transesophageal echocardiography in hemodynamically unstable patients. *Mayo Clinic Proceedings* 1995; **70**: 925–931.
14. Hodgins L, Kisslo JA, Mark JB. Perioperative transesophageal echocardiography: the anesthesiologist as cardiac diagnostician. *Anesthesia and Analgesia* 1995; **80**: 4–6.
15. Practice guidelines for perioperative transesophageal echocardiography. A report by the American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology* 1996; **84**: 985–1006.

Haemodilution induces a hypercoagulable state

Sir,—Ruttmann, James and Viljoen[1] have described the effects of haemodilution on *in vitro* coagulation using the TEG, and among their conclusions suggested that 20% dilution with isotonic saline increases absolute clot strength, while at the same dilution with Haemaccel (3.5% polygeline solution) clot strength is unaltered. We have recently published similar work,[2] but with a range of dilutions (15, 30, 45, 60 and 75%). We found that both the size (clot weight) and strength (using maximal amplitude on the TEG) of clots formed *in vitro* were reduced considerably with increasing dilutions of both Haemaccel and Gelofusine (4% succinylated gelatin) compared with the same dilutions with saline or Ringer's solution. Scanning electron microscopy of these clots showed a reduction in cross-linkage with the colloids compared with dilution with saline, or controls from undiluted blood. This could be explained by an effect on fibronectin, as other workers have shown that gelatin binds to fibronectin[3] and that infusion of these fluids decreases plasma concentrations of fibronectin.[4] Although Ruttmann, James and Viljoen emphasized that their study did not examine greater or lesser degrees of dilution, our findings raise concern where large volumes of these fluids are given to patients requiring full haemostatic competence, and we endorse his suggestion that *in vivo* studies using the TEG should take place in patients receiving different fluid regimens.

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1. Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *British Journal of Anaesthesia* 1996; 76: 412–414.
2. Mardel SN, Saunders F, Ollerenshaw L, Edwards C, Baddeley DT. Reduced quality of in-vitro clot formation with gelatin based substitutes. *Lancet* 1996; 347: 825.
3. Engvall E, Ruo-Slahti E, Miller VJ. Affinity of fibronectin to collagens of different genetic types and fibrinogen. *Journal of Experimental Medicine* 1978; 147: 1584.
4. Brodin B, Hesselvik F, von-Schenck H. Decrease of plasma fibronectin concentration following infusion of a gelatin based plasma substitute in man. *Scandinavian Journal of Clinical Laboratory Investigation* 1984; 44: 529.

Sir,—Mardel and colleagues[1] reported on a study comparing the effects of various dilutions of blood with crystalloid with those with colloid. They found some inhibition of clot maturation, as measured by clot strength, in the colloid group and attributed this effect to the binding of fibronectin to the gelatin molecule. In this respect their results are in agreement with our findings.[2]

However, we are confused by the assertion that "scanning electron microscopy of these clots showed a reduction in cross-linkage with the colloids compared with dilution with saline, or controls from undiluted blood". Careful reading of the report of Mardel and colleagues shows that their controls were diluted with saline or Ringer's lactate. Nowhere do they mention an undiluted control.

It is our contention that haemodilution with crystalloid is not inert but activates some aspects of coagulation in an as yet undefined manner. It is therefore difficult to interpret coagulation studies in which haemodilution with crystalloid is used as a control as these do not necessarily show that gelatin haemodilution *per se* causes reduced clot strength compared with the native condition.

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1. Mardel SN, Saunders F, Ollerenshaw L, Edwards C, Baddeley DT. Reduced quality of in-vitro clot formation with gelatin based substitutes. *Lancet* 1996; 347: 825.
2. Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *British Journal of Anaesthesia* 1996; 76: 412–414.

ERRATUM

British Journal of Anaesthesia 1996; 77: 312–316.

The first author of the article is S. Al Ramadhani and not S. A. L. Ramadhani as published. Also, Dr Ramadhani's qualification is FFARCSI and not FRCA.

We apologize for this confusion.

British Journal of Anaesthesia 1996; 77: 702–703

BOOK REVIEWS

Clinical Anaesthesia. A. R. AITKENHEAD AND R. M. JONES (editors). Published by Churchill Livingstone, Edinburgh. Pp. 780; indexed; illustrated. Price £85.00.

Professors Aitkenhead and Jones, those indefatigable editors, have produced a new, short textbook of clinical anaesthesia. They argue in the preface that most textbooks have grown too large and have become too expensive, as they attempt to cover all aspects of the relevant basic sciences and clinical practice. The present text aims to provide a concise account of clinical anaesthesia in the 1990s and is intended for an international readership. Twenty-three of the 41 authors are from the UK, 10 from USA, seven from Europe and one from Australia. Among the authors are many with an international reputation: Booij, Breivik, Coriat, Cunningham, Fitch, Frost, Hug, Lindahl, Pollard, Reiz, Runciman, Sear and White, together with young co-authors who may well join this group in the future. The editors had a laudable aim and were able to recruit good authors, so does it work in practice?

The book contains 30 chapters and only 15 of these are devoted to anaesthesia for specific surgical areas, such as cardiac surgery and paediatric surgery. The other chapters cover topics such as preoperative assessment, monitoring, postoperative pain relief, safety, and audit and quality assurance. The last, short chapter by Lunn on "the quest for quality – how to keep up to date" is an idiosyncratic, but highly successful, way to finish. Most chapters are extensively referenced, and in some instances this is excessive. The prize for "referencitis" goes to Breivik and Bogod who found it necessary to use 277 references in a chapter on obstetric analgesia and anaesthesia. This is followed closely by the 264 references cited in a 10-page chapter on cardiopulmonary resuscitation. The ease of access to the anaesthetic literature does nothing to help find quality among quantity.

A few chapters are strangely unconvincing. A chapter that covers one of my major, clinical commitments gave an excellent review of the underlying physiological problems, but was of no value in dealing with common intra- and postoperative difficulties. I was left with the strong impression that the distinguished authors were lacking in recent, practical experience.

The space devoted to certain anaesthetic problems fails to reflect their current, clinical importance. Laparoscopic cholecystectomy is dealt with in half a page, which is slightly more than pancreatic surgery, but at least hepatic surgery merits two pages. Key areas of anaesthetic practice, such as anaphylaxis, are also dealt with in two pages, however the index helped in finding other relevant information about this topic. Do not rely on the index to help you learn about MH; the pages indicated will refer you to a discussion on training devices and anaesthetic simulators!

Overall, the book is competently produced with few errors and is priced competitively. I do not think that it quite hits the target. Nevertheless, the idea is thoroughly sound and I urge the editors and authors to persevere – promising but must improve.

G. M. Hall

Peripheral Nerve Blockade. C. A. PINNOCK, H. B. J. FISCHER AND R. P. JONES. Published by Churchill Livingstone, Edinburgh. Pp. 174; indexed; illustrated. Price £29.50.

There is growing interest in the application of peripheral nerve blocks for an increasing variety of surgical procedures. This book sets out to be very much a comprehensive, practical manual serving both trainee and experienced practitioner alike. The text is clear and concise, and the layout facilitates rapid access to the relevant information with great emphasis placed on the excellent line drawings. It is clear to any regional anaesthesia enthusiast that the authors themselves have considerable practical experience in this field, allowing them to give practical guidance in addition to highlighting areas of controversy as and when they occur within the text.

The first short section deals with the essentials of principles and practice, concentrating on benefits, methods and hazards, while the second section deals with the applied anatomy of the various operative sites and the possible surgical indications. Section three deals with the nerve blocks themselves. I assessed the aims of this section by looking first for a few specific "useful" blocks for day-case surgery or the medically compromised patient and was not disappointed. Field block for mesh inguinal hernia repair, inguinal canal block, arthroscopy block, ophthalmology blocks and even the sustentaculum tali block for those particularly compromised vascular patients, are all well covered.

The major nerve blocks of upper and lower limb are also well described as one would expect, although the technique of axillary block outlined is very much one of many. Techniques for using the nerve stimulator at this or the mid-humoral level could possibly have been included, although this may not have reflected the authors' own personal expertise. For the experienced practitioner it is always useful to have a handy reminder of blocks at the elbow and wrist in case one day one might need to supplement! The line drawings are particularly useful in this section. A short discussion on evolving catheter techniques outlines further possibilities for a variety of blocks with a view to postoperative pain relief, and there is comprehensive coverage of head and neck blocks.

While no substitute for practical tuition, overall this is an excellent addition to the recent publications on regional anaesthesia. As I had hoped, this book points out the major contribution of peripheral blocks in the management of postoperative pain but still concentrates on the art of regional anaesthesia as the sole technique for surgical intervention and not as a hit or miss supplement to general anaesthesia. It would clearly be invaluable to examination candidates but its concise and practical layout and size suggest that its prime location should not be the library bookshelf but the duty room of any (or every) theatre suite. I can think of few better for this purpose.

D. M. Coventry

Clinical Intensive Care. K. HILLMAN AND G. BISHOP. Published by Cambridge University Press, Cambridge. Pp. 835; indexed; illustrated. Price £35.00.

Intensive care medicine is changing very rapidly; there are changes occurring constantly in response to good science in addition to fashion and politics. Therefore, much that is written will be out of date by the time the book is published.

Of the 32 chapters of this book, the first third cover mainly general concepts. The authors lose their way here, inaccurate generalities occur and detailed dogmas that I disagree with appear often. Resuscitation procedures and specific antibiotic guidelines are not helpful. In particular when the guidelines differ from the European Resuscitation Council guidelines this could be disastrous for trainees preparing for examinations. I disagree with statements on nutrition, fluid balance, the stated importance of fluid restriction in ARDS and the importance of peripheral oedema as a problem.

The second part of the book examining particular organ systems and clinical problems was much better. The chapters on thoracic trauma, intracranial disasters and acute renal failure were very clear, readable and succinct. There are some very good axioms, and also some good tables and diagrams. Bold checklists covering some common situations are well conceived.

In its present form the book falls between two stools; as a reference text it would need further expansion and authority but it misses the mark as a handbook for trainees, and inaccuracies, repetition and unnecessary detail swamp the good material.

W. Russell

A Practical Approach to Pain Management. M. LEFKOWITZ AND A. H. LEBOVITS (editors). Published by Little, Brown and Co., Boston. Pp. 310; indexed; illustrated. Price £29.50.

This volume of some 310 pages attempts to cover the whole aspect of pain management using the "cook book" type of presentation. Consequently, because of the need for brevity, each word needs to be selected with extreme care such that each imparts the maximum information while taking up the minimum of space. In such a situation, to try and cover the whole of pain management requires extreme care on the part of the authors and utter ruthlessness on the part of the editors. Unfortunately, this volume suffers from a lack of direction and control from the latter to the former and, therefore, ends up as an uneven and somewhat uninteresting compilation.

The book is divided into two parts: therapeutic and diagnostic approaches and pain syndromes. The former is subdivided into six parts dealing with acute pain, pharmacological management, regional techniques, psychological approaches, physical techniques and other approaches to chronic pain management. The latter deals with many major areas of pain, including that due to cancer, low back and phantom limb, pain in children, herpes zoster and post-herpetic neuralgia, to mention but five of 16.

The book aims to provide the busy single specialty provider with a detailed and in depth review of the significant clinical practice approaches in pain management. On the other hand the editors write that it is not intended as a comprehensive textbook, rather it is a "how to" handbook written in outlined format. There does appear to be a hint of confusion here.

There are 46 contributing authors, nearly all of whom work in the eastern USA, thereby giving this tome a distinctive flavour. None the less, they have a good attempt at answering the editors' demands. However, as would be expected, there are both omissions and commissions. There is a plethora of words, too many of which are space wasters and do not contribute to the education of the reader. The illustrations are mediocre, basic and unnecessary taking up page space that could have been better used for good flow charts, diagrams, etc. The chapters are variable, not only in content, but also in length, references and value.

For a 1996 first edition, there is insufficient modern contemporary thought and therapy. Surprisingly, no mention is made of NMDA and substance P antagonists, bradykinin, dorsal root ganglion injections and Harkensen's technique, whereas cocaine, benzocaine and several other virtually obsolete agents feature, in some cases, with marked prominence.

Many of the tables of drugs can be obtained elsewhere and have been produced better in that situation. Also, precise descriptions of techniques are unnecessary in such a book and yet they appear, sometimes with embarrassing detail that can be better obtained from the specialist manuals that are all too rarely referenced.

Even at £29.50, this is not a book that one could encourage trainees to buy, but rather to peruse in the library and then place back on the shelf before moving on to what will inevitably be a better text

K. Budd

Cardiac Arrest. The Science and Practice of Resuscitation Medicine. N. A. Paradis, H. R Halperin and R. M. Nowak (editors). Published by Williams and Wilkins, Pp. 981; indexed; illustrated. Price £125.00.

This major work on the science and art of resuscitation medicine is unique in that it not only reviews the literature past and present, but also provides a reasoned description of the current state of the art and a look to the future. The is a multi-author text, drawing its writings from over 90 authors in 53 chapters. Most of the authors are from North America and are well known in the field of resuscitation. All of the authors have obviously been well briefed as to their task by the three named editors of the book and there is little repetition in the text.

The first section describes the history and epidemiology of sudden death. It is interesting that the authors of both these chapters sum up by reflecting on the lack of information available on the true physiology and pharmacology of this science. This leads neatly on to the second section where there are chapters on basic science. Most of this section reviews cell death and reperfusion. It also includes a fascinating section on the methodology of cardiopulmonary resuscitation research and provides many of the basic facts of how to carry out this form of research using modern scientific instrumentation.

Section three continues the global ischaemia and reperfusion story with seven chapters on pathophysiology and aetiology. In this section there are three detailed individual chapters on the aetiology, electrophysiology and mechanics of ventricular fibrillation, pulseless electrical activity and bradyasystolic states. Together they help to clear a path through the established jungle of anecdotal medicine associated with resuscitation. Section four deals with the therapy of sudden death and although the 17 chapters discuss all the relevant aspects of therapy, they are heavily biased towards the North American procedures and say little, if anything, about other national procedures.

Section five, special circumstances, has chapters on neonatal and paediatric resuscitation, the elderly patient, asphyxial, haemorrhagic, hypovolaemic, hypothermic and toxicological sudden death. It also deals with cardiac arrest during anaesthesia and in pregnancy, in the drowned and in the electrocuted patient. This is one of the best sections in the book as the authors have managed to assimilate and digest a wide range of publications and viewpoints and bring them together into a well-reasoned argument on the therapy of these rarer resuscitation scenarios. Section six has six chapters on post resuscitation disease. It includes a chapter on post-resuscitation prognostication and the declaration of brain death. It highlights the difficulties found at the sharp end of clinical practice of deciding when to stop resuscitation and how to deal with the initial resuscitation success which subsequently turns into the long-term intensive care patient. Its arguments are useful to those who have to battle against colleagues who declare all resuscitation events as failures despite their aetiological background.

The final section and chapter deals with the future and development of informational guidelines for practising and reporting resuscitation events. It points out that despite there being a single foundation of published research, national bodies have produced different regimens, often depending on internal political pressures. An international body does exist to rectify this matter and this chapter formulates the basic strategy on which this body is now formulating international recommendations on resuscitation.

The book is extremely well written, referenced and indexed. It is illustrated appropriately and each illustration is fully referenced. If I must have one criticism it is, as stated above, that it is biased heavily to the science and art based around the North American regimens. This may account for the complete lack of any reference to the use of the laryngeal mask airway in resuscitation. It is harder to explain the inclusion of only one and one half columns on automated external defibrillation as this is one of the foremost developments in this field; it may reflect how rapidly resuscitation has moved forward during the time of compiling and publishing this text.

This is a must for everyone interested in or researching resuscitation. Although its price is high, this can be justified as it is one of the most complete reference sources on resuscitation in the current published literature. In fact, it has hardly sat on my library shelf as I find myself constantly referring to it for both references and comments. I highly recommend this book.

D. A. Zideman

Core Curriculum for Professional Education in Pain, 2nd Edn. H. L. Fields (editor). Published by IASP Press, Washington. Pp. 123; indexed. Price $25.00.

This is the second edition of *Curriculum for Education in Pain*; the first addition apperared in 1991. The document was developed by a task force of international specialists from a broad discipline base in pain management, including neurology, oncology, rehabilitation medicine, psychiatry, rheumatology and the basic sciences. It is aimed for use as a reference for other curricula for designing training programmes and as a basis for rationalizing and planning patient services.

The curriculum is divided into chapters, each covering various topics from the pharmacology of pain transmission and pain measurement, through to specific disease states, including low back pain, myofascial pain and cancer pain. Its format consists of headings and lists of relevant areas in each topic. There is a helpful chapter on designing, reporting and interpreting clinical trials in the management of pain, and a good, up-to-date bibliography.

The book is an improvement on the first edition and takes account of the brisk pace of expansion of the knowledge base in the field of pain research in recent years. It is a useful publication for those responsible for designing training programmes and patient services in pain management.

M. E. Bone

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Ether anaesthesia comes to London. December 1846

In October of this year, 1996, the sesquicentenary of the first successful public demonstration of ether anaesthesia by William Thomas Green Morton was celebrated in Boston, in appropriate style. It is rare for any discovery to be attributable to only one individual and the very different roles of Crawford Long, Horace Wells and Charles T. Jackson have been well aired over many years. Morton, nevertheless, was the figure of the day. Described by Jacob Bigelow as "not a human of much cultivation or science", one can easily conjure a picture of a relatively humble journeyman dentist arriving by invitation at the Massachusetts General Hospital for a demonstration that, in the light of previous failure by others, might not attract a totally confident assembly. Dr Barbara Duncum[1] quotes from N.P. Rice's *Trials of a Public Benefactor* published in 1859:

"He (Morton) had taken the precaution to request Mr Frost to accompany him, to conduce in some way to his relief, in case of failure and act as a voucher as regards his statements of what he had already accomplished. At this moment his mind was in one great whirl of doubts and conflicting emotions."

Morton was ambitious but he was also brave.

In Britain, news of ether anaesthesia did not arrive until the penultimate week of the year. Against today's sophisticated communications the use of Francis Boott as an intermediary between Jacob Bigelow and Robert Liston, by this time a leading surgeon of London, seems unusual. Yet Boott acted effectively and swiftly. Not only did Liston operate successfully under ether anaesthesia within the space of 5 days but Boott's association with James Robinson, a leading London dentist, led to Robinson's successful demonstration on December 19, the Saturday before Liston's successful operation on the following Monday. It is customary to note the "Dumfries claim" in which the news was brought to Scotland, faster than to London, by a local doctor who had travelled from Boston to Dumfries via Liverpool. Sadly the outcome, whatever is was, adds nothing to either science or medicine as the public announcement was some 20 years delayed and there is no trace of the patient!

Before the year ended, John Snow who became the leading figure in the development of ether anaesthesia had attended one of Robinson's administrations. James Young Simpson, the Professor of Midwifery at Edinburgh, had journeyed in the Christmas holiday period to London, probably to visit Liston, for the specific purpose of learning about ether anaesthesia. Simpson took the news north and, with the shared interest of several of his contemporaries at Edinburgh, became an immediate enthusiast for anaesthesia and moved quickly, if controversially, to the use of ether for the relief of the pain of difficult labour.

By today's standards it seems quite remarkable that Robinson, and soon Snow, appeared so rapidly and effectively in print on their contributions and perceptions in respect of the new discovery. While the unfortunate Morton's star was soon in decline as he struggled unsuccessfully to assert his ownership of, and explore a patent for, ether, John Snow was the man in the right place at the right time to develop the scientific basis of anaesthesia which he did to superb effect. There can be little doubt that the explanation for this zeal and success lay not only in Snow's rather puritanical character but equally his strong motivation to ensure that as a doctor in 19th century England he was equipped with the highest academic qualifications. In time for the sesquicentenary of ether anaesthesia, Dr David Shephard, from Prince Edward Island, Canada, has produced a new biography of John Snow which, although populist in places, provides an excellent resource on an important medical pioneer.[2]

Of the British pioneers, Robinson, Snow and Simpson, it is notable that all three were leaders in their profession and would have enjoyed such a position even if they had made no contribution to anaesthesia. At a time when dentistry could offer very little in the way of control of the quality of practice, Robinson enjoyed the highest reputation as a practitioner, with a distinguished clientele which included Prince Albert The Prince Consort. Indeed it is interesting to consider that Albert's contact with Robinson would have been at least one reliable source of intelligence about anaesthesia which ultimately led to chloroform analgesia being sought by Queen Victoria from John Snow in 1853 and again in 1857, although on the second occasion either the Queen was early or Snow was late. He arrived to find Prince Albert administering the chloroform!

Snow as a respected practitioner in Soho and as an enthusiastic participant of medical and scientific societies is, or should be, remembered for his study and recognition of putrid water as the source of cholera several years before Pasteur. Similarly, Simpson advocated "hospitalism" based on the recognition that a fever developed after injury was often less serious outside compared with inside a hospital. He, too, was several years ahead of Lister, with strongly expressed views on how hospitals should be designed (and regularly destroyed and rebuilt); all this in addition to his laying the foundations of gynaecological practice and his distinction as an antiquarian. Perhaps it was because of these polyglot characteristics among the pioneers that the "science" of anaesthesia in Britain was subject to stewardship of a high order, and the general acceptance of the clinical use of anaesthesia, although occasionally the subject of controversy, was remarkably trouble free.

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References

1. Duncum, Barbara M. *The Development of Inhalation Anaesthesia.* London: Oxford University Press, 1947; 109.
2. Shephard D. *John Snow. Anaesthetist to a Queen and Epidemiologist to a Nation. A Biography.* Cornwall, Prince Edward Island, Canada: York Point Publishing, 1995.

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EDITORIAL II

Is it always necessary to antagonize residual neuromuscular block? Do children differ from adults?

Use of an anticholinesterase at the end of surgery, to antagonize residual neuromuscular block induced by a non-depolarizing drug, is commonplace; it is easy to forget that such drugs were not always given routinely. When the clinical use of "Intocostrin" (a biologically standardized extract of curare) was first described in 25 patients by Griffith and Johnson in 1942, it was only recommended that an ampoule of the antidote, prostigmine, be readily available[1]; there was no mention of administering the antagonist. Indeed, it is difficult to determine how anticholinesterases came into regular use.[2] Neostigmine was noted only to be given "seldomly" by Prescott and colleagues in 1946, in doses of up to 5 mg, even though these workers were using tubocurarine 0.4 mg kg^{-1} for abdominal surgery.[3] Undoubtedly, failure to use an anticholinesterase was a factor in the morbidity associated with the use of small doses of non-depolarizing neuromuscular blocking drugs in patients breathing spontaneously, and a reason why such techniques fell into disrepute in the early 1950s.[4] Unfounded fears of neostigmine causing cardiac arrest were probably a reason for its omission.[5] With the increasing use of larger doses of tubocurarine or pancuronium and controlled ventilation many, although not all, clinicians began to administer neostigmine 5 mg to adults.[5 6] Large doses of anticholinesterase were used in children at this time: neostigmine 0.08 mg kg^{-1} was given to antagonize tubocurarine in neonates, who were thought to need an even higher dose than adults to obtain reliable recovery.[7]

With the advent of the intermediate-acting non-depolarizing agents, atracurium and vecuronium, the need for such high doses of anticholinesterase was questioned.[8] Clinicians soon realized that recovery from these agents was more rapid than with tubocurarine or pancuronium. The greater clearance of the newer drugs from plasma, and hence a more rapid decrease in relaxant concentration at the post-synaptic nicotinic receptor allowed, on some occasions, for the omission of an anticholinesterase. This has some benefits; nausea and vomiting may be less common in patients who are not given neostigmine after the use of a non-depolarizing drug.[9] Any detrimental effect of neostigmine on a newly created gut anastomosis can also be avoided.[10]

But careful monitoring of neuromuscular block is always necessary if anticholinesterases are not used. It is well recognized that even the clinicians most experienced in using monitoring techniques cannot detect decrement of the train-of-four twitch response by visual or tactile means, when the fourth twitch of the train has recovered to more than 40% of the first.[11] It is essential therefore for all anaesthetists to quantify the train-of-four ratio if they are considering not using an anticholinesterase. Double burst stimulation, which consists of two or three bursts of 50 Hz tetanus, 750 ms apart, is thought to be more useful in detecting fade by visual or tactile means than the train-of-four response, although the differences are marginal.[12] In addition, it is now thought that 80% recovery of the train-of-four ratio T4/T1 (and not 70% as first described[13]), is a more reliable indicator of adequate recovery if electromyographic monitoring is used.[14] This degree of spontaneous recovery may take much longer than is appreciated, even with atracurium or vecuronium. For example, the average time to spontaneous recovery of T1/T0 to 95% after atracurium 0.5 mg kg^{-1} is 68 min.[15] But it is probable that with atracurium and vecuronium, neostigmine 2.5 mg in adults is an unnecessarily large dose to antagonize residual block, if greater than 20% recovery of T1/T0 has already occurred.[16 17] Doses of neostigmine 1.25 mg are almost as effective. Even neostigmine 0.625 mg accelerates recovery after atracurium, although not after vecuronium.[17]

The introduction of mivacurium, which is metabolized by plasma cholinesterase, again raised the question of whether or not it was always essential to antagonize residual block. Neostigmine, although not edrophonium, was known to inhibit plasma cholinesterase activity,[18 19] and it was therefore postulated that neostigmine may *potentiate* mivacurium-induced neuromuscular block. There has been little evidence of such an effect,[20] although neostigmine would only seem to speed recovery from mivacurium-induced block by a few minutes.[21] The mean time for spontaneous recovery of T1/T0 from 25 to 75% (the recovery index) after a constant infusion of mivacurium is 7.7 min; if neostigmine 35 $\mu g\ kg^{-1}$ is administered at 20% recovery of T1/T0, the recovery index is only reduced to 4.7 min. However, a few minutes add up to a long time if 10 laparoscopies are performed on a half-day list!

Plasma cholinesterase activity is greater in children than in adults and this is thought to explain the more rapid spontaneous recovery from mivacurium-induced neuromuscular block in the young.[22 23] Whether mivacurium is given as a single bolus dose or by constant infusion in children, the benefit of using an anticholinesterase to speed recovery is questionable (if neuromuscular monitoring is being used), and edrophonium is a more appropriate agent than neostigmine to antagonize any residual block.[24]

The longer-acting, non-depolarizing agents which are cleared more slowly from plasma have, of necessity, been antagonized routinely. But in children, Fisher and colleagues demonstrated that the dose–response curve for neostigmine, although not edrophonium, used to antagonize residual block from tubocurarine, was shifted to the left of that in adults,[25 26] for the first time disputing the belief that larger doses of anticholinesterase were needed in the younger age group. As the distribution volumes and distribution half-lives of neostigmine and edrophonium are similar in all age groups, these differences cannot be explained easily by a pharmacokinetic mechanism.[25 26] It was postulated that local differences at the neuromuscular junction in children, such as the number of nicotinic receptors, amount of acetylcholine reserve or acetylcholinesterase activity, may be the causes of the lower dose requirements for anticholinesterases in paediatric patients.[26] In addition, a more rapid circulation time in children speeds both delivery of anticholinesterase to the neuromuscular junction, hastening onset of effect, and also increases its rate of removal, shortening the duration of action. There is evidence, however, that it is the more rapid removal of the *relaxant* from the neuromuscular junction that is responsible for the more rapid recovery from block in children.[24]

Antagonism of neuromuscular block induced by pancuronium or doxacurium may be achieved with relatively smaller doses of neostigmine or edrophonium in children than in adults.[27] Recovery rates from both blockers were similar in this study but in children, only half the weight-related dose of neostigmine or edrophonium used in adults was needed to produce the same effect. In an older study of recovery from pancuronium-induced neuromuscular block in children and adults, recovery of T1/T0 was found to be faster after large doses of edrophonium (1.43 mg kg^{-1}) than after a large dose of neostigmine (0.071 mg kg^{-1}) in all ages of children.[28] Whichever anticholinesterase was used, recovery was more rapid in children than in adults.

In this issue, recovery from rocuronium-induced neuromuscular block is reported in children and in adults during isoflurane anaesthesia, using varying doses of neostigmine.[29] Small doses of neostigmine after rocuronium 0.6 mg kg^{-1} have a more marked effect in children aged 2–10 yr; for example, 5 μg kg^{-1} produced as rapid a recovery of T4/T1 to 0.7 in children as neostigmine 50 μg kg^{-1} in adults. These findings are impressive and, if substantiated, could alter paediatric anaesthetic practice significantly. Unlike mivacurium,[24 30] spontaneous recovery in children and adults after rocuronium was at least twice as long as that induced by neostigmine 50 μg kg^{-1}. In children aged 1–5 yr during halothane anaesthesia, spontaneous recovery of T4/T1 to 0.75 after rocuronium 0.6 mg kg^{-1} had previously been shown to occur in a mean time of 41.9 min, which is a shorter time than in adults.[31] Of note is the wide range of recovery of T4/T1 to 0.75 (26.5–57.7 min). Such wide variation with the aminosteroid neuromuscular blocking agents is an indication for always using at least a small dose of anticholinesterase when these drugs are administered. It has been suggested, in an interim report, that recovery from rocuronium-induced neuromuscular block is slower in young children aged 1–4 yr than in older children aged 5–10 yr during halothane anaesthesia.[32] Neostigmine administered at 25% recovery of T1/T0 again halved the recovery index (25–75% T1/T0) in both age groups. Further work is necessary on the pharmacokinetics and pharmacodynamics of rocuronium in children of all ages.

Nevertheless, it is becoming clear that, after administering the newer neuromuscular blocking agents, anaesthetists should again question if they are using too much neostigmine. If neuromuscular block is being monitored, and recovery is established (e.g. all four twitches of the train-of-four response are present), neostigmine 2.5 mg may be unnecessary in an adult who has received atracurium or mivacurium. Neostigmine 1.25 mg may be preferable. Decreasing the dose of the anticholinesterase may reduce its side effects. In children, smaller doses of anticholinesterase are necessary, even after using the aminosteroid neuromuscular blocking drugs, and especially with mivacurium, when they may not be needed at all!

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References

1. Griffith HR, Johnson GE. The use of curare in general anesthesia. *Anesthesiology* 1942; **3**: 418–420.
2. Utting JE. The era of relaxant anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 551–553.
3. Prescott F, Organe G, Rowbotham S. Tubocurarine chloride as an adjunct to anaesthesia. *Lancet* 1946; **2**: 80–84.
4. Beecher HK, Todd DP. A study of the deaths associated with anaesthesia and surgery. *Annals of Surgery* 1954; **140**: 2–34.
5. Riding JE, Robinson JS. The safety of neostigmine. *Anaesthesia* 1961; **16**: 346–354.
6. Katz RL. Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. *Anesthesiology* 1967; **28**: 327–336.
7. Bush GH, Stead AL. The use of d-tubocurarine in neonatal anaesthesia. *British Journal of Anaesthesia* 1962; **34**: 721–728.
8. Astley BA, Katz RL, Payne JP. Electrical and mechanical responses after neuromuscular blockade with vecuronium, and subsequent antagonism with neostigmine or edrophonium. *British Journal of Anaesthesia* 1987; **59**: 983–988.
9. King MJ, Milazkiewicz R, Carli F, Deacock AR. Influence of neostigmine on postoperative vomiting. *British Journal of Anaesthesia* 1988; **61**: 403–406.
10. Ogilvy AJ, Smith G. The gastrointestinal tract after anaesthesia. *European Journal of Anaesthesiology* 1995; **10S**: 35–42.
11. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemmer-Jorgensen B. Tactile and visual evaluation of the response to train-of-four nerve stimulation. *Anesthesiology* 1985; **63**: 440–443.
12. Engbaek J, Ostergaard D, Viby-Mogensen J. Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block. *British Journal of Anaesthesia* 1989; **62**: 274–278.
13. Ali HH, Utting JE, Gray TC. Quantitive assessment of residual antidepolarising block (Part 1). *British Journal of Anaesthesia* 1971; **43**: 473–477.
14. Engbaek J, Ostergaard D, Viby-Mogensen J, Skovgaard LT. Clinical recovery and train-of-four ratio measured mechanically and electromyographically following atracurium. *Anesthesiology* 1989; **71**: 391–395.
15. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarising muscle relaxant. *Anesthesia and Analgesia* 1982; **61**: 723–729.
16. Harper NJN, Wallace M, Hall IA. Optimum dose of neostigmine at two levels of atracurium-induced neuromuscular block. *British Journal of Anaesthesia* 1994; **72**: 82–85.
17. Jones JE, Parker CJR, Hunter JM. Antagonism of blockade produced by atracurium or vecuronium with low doses of neostigmine. *British Journal of Anaesthesia* 1988; **61**: 560–564.
18. Mirakhur RK, Lavery TD, Briggs LP, Clarke RSJ. Effects of neostigmine and pyridostigmine on serum cholinesterase activity. *Canadian Journal of Anaesthesia* 1982; **29**: 55–58.
19. Mirakhur RK. Edrophonium and plasma cholinesterase activity. *Canadian Journal of Anaesthesia* 1986; **33**: 588–590.

20. Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 393–399.
21. Phillips BJ, Hunter JM. Use of mivacurium chloride by constant infusion in the anephric patient. *British Journal of Anaesthesia* 1992; **68**: 492–498.
22. Goudsouzian NG, Alifimoff JK, Eberly C, Smeets R, Griswold J, Miller V, McNulty BF, Savarese JJ. Neuromuscular and cardiovascular effects of mivacurium in children. *Anesthesiology* 1989; **70**: 237–242.
23. Bevan JC, Tousigant C, Stephenson C, Blackman L, Reimer E, Smith MF, Bevan DR. Dose responses for neostigmine and edrophonium as antagonists of mivacurium in adults and children. *Anesthesiology* 1996; **84**: 354–361.
24. Bevan DR, Kahwaji R, Ansermino JM, Reimer E, Smith MF, O'Connor GAR, Bevan JC. Residual block after mivacurium with or without edrophonium reversal in adults and children. *Anesthesiology* 1996; **84**: 362–367.
25. Fisher DM, Cronnelly R, Miller RD, Sharma M. The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983; **59**: 220–225.
26. Fisher DM, Cronnelly R, Sharma M, Miller RD. Clinical pharmacology of edrophonium in infants and children. *Anesthesiology* 1984; **61**: 428–433.
27. Bevan JC, Purday JP, Reimer EJ, Bevan DR. Reversal of doxacurium and pancuronium neuromuscular blockade with neostigmine in children. *Canadian Journal of Anaesthesia* 1994; **41**: 1074–1080.
28. Meakin G, Sweet PT, Bevan JC, Bevan DR. Neostigmine and edrophonium as antagonists of pancuronium in infants and children. *Anesthesiology* 1983; **59**: 316–321.
29. Abdulatif M, Mowafi H, Al-Ghamdi A, El-Sanabary M. Dose–response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults. *British Journal of Anaesthesia* 1996; 77; 710–715.
30. Naguib M, Abdulatif M, Al-Ghamdi A, Hamo I, Nouheid R. Dose–response relationships for edrophonium and neostigmine antagonism of mivacurium-induced neuromuscular block. *British Journal of Anaesthesia* 1993; 71: 709–714.
31. Woelfel SK, Brandom BW, Cook DR, Sarner JB. Effects of bolus administration of Org-9426 in children during nitrous oxide–halothane anesthesia. *Anesthesiology* 1992; **76**: 939–942.
32. Motsch J, Leuwer M, Böttiger BW, Bach A, Schönstedt R, Martin E. Dose–response, time course of action and recovery of rocuronium bromide in children during halothane anaesthesia. *European Journal of Anaesthesiology* 1995; 12 (Suppl. 11): 73–78.

British Journal of Anaesthesia 1996; 77: 710–715

CLINICAL INVESTIGATIONS

Dose–response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults

M. ABDULATIF, H. MOWAFI, A. AL-GHAMDI AND M. EL-SANABARY

Summary

Dose–response relationships for the antagonism of intermediate-acting neuromuscular blocking agents have not been evaluated previously in children. We have examined the dose–response relationships for neostigmine antagonism of 90% rocuronium-induced neuromuscular block in children and adults, during nitrous oxide–1 MAC of isoflurane anaesthesia. We studied 40 children, aged 2–10 yr, and 50 adults, aged 18–60 yr; all received a single bolus dose of rocuronium 0.6 mg kg^{-1} and accelerometry was used to monitor neuromuscular transmission. When the first twitch of the train-of-four (TOF) response (T1) recovered to 10% of its control (T0), one of five doses of neostigmine 0, 5, 10, 20 or 50 μg kg^{-1} was given by random allocation to each of the study groups (*n*=8 children and *n*=10 adults). Recovery of T1 and TOF ratio (T4/T1%) was recorded for 10 min after initial administration of neostigmine. Onset time of rocuronium-induced block was faster in children than in adults (mean 64.6 (95% confidence intervals 57.7–71.5) s *vs* 83.7 (70.7–96.6) s; $P<0.05$). The time to 10% recovery of T1/T0 was shorter in children than in adults (25.4 (22.9–27.9) min *vs* 38.8 (36.1–41.4) min; $P<0.001$). Spontaneous and antagonist-assisted recovery were more rapid in children than in adults. Adequate recovery (T4/T1 of 80%) occurred in children at 4, 5 and 8 min after neostigmine 50, 20 and 10 μg kg^{-1}, respectively. Adequate recovery was not produced in adults by any dose of neostigmine within 10 min. The effective doses of neostigmine required to achieve a TOF ratio of 80% (ED_{80}) after 10 min in children and adults were, respectively, 7.10 (5.2–9.8) μg kg^{-1} and 56.56 (45.5–71.9) μg kg^{-1} ($P<0.001$). There was no advantage in administering doses of neostigmine greater than 20 μg kg^{-1} to antagonize 90% rocuronium-induced neuromuscular block in children. In contrast, it appeared prudent to use neostigmine 50 μg kg^{-1} or more for adequate antagonism of a similar degree of block in adults. (*Br. J. Anaesth.* 1996; **77**: 710–715)

Key words
Anaesthesia, paediatric. Antagonists neuromuscular block, neostigmine. Neuromuscular block, rocuronium. Age factors. Pharmacology, dose–response.

In the past, there was an undocumented belief that higher doses of neostigmine were required for adequate antagonism of long-acting neuromuscular blocking drugs in children.[1] Later dose–response studies, however, showed that the dose of neostigmine required to antagonize tubocurarine-, pancuronium- or doxacurium-induced blocks in children was in the range of 25–50% of the adult value.[2 3] Also, in a recent dose–response study of mivacurium antagonism, Bevan and colleagues[4] reported that, compared with adults, children had a very rapid rate of spontaneous recovery to the extent that 10 min after antagonism with edrophonium or neostigmine, recovery in children was not very different from spontaneous recovery. In a subsequent study, the same group proved that it was safe to omit antagonism at the end of mivacurium-induced neuromuscular block in children but not in adults.[5]

Several dose–response studies have evaluated antagonism of intermediate-acting neuromuscular blocking drugs with anticholinesterases in adults.[6 7] Single-dose studies of neostigmine antagonism of vecuronium-induced block have demonstrated that the rate of recovery is age-dependent, being more rapid in children than in infants and adults.[8] However, single-dose comparisons between adults and children may be misleading and dose–response studies are a more appropriate alternative.[6] To date, antagonist dose–response studies have not been carried out for intermediate-acting neuromuscular blocking agents in children. Therefore, this study was designed to construct and compare the dose–response curves for neostigmine antagonism of an equivalent degree of neuromuscular block induced by the recently introduced intermediate-acting non-depolarizing neuromuscular blocker, rocuronium, in children and adults under similar anaesthetic conditions.

Patients and methods

We studied 40 children, aged 2–10 yr (mean 5.3 yr) and weighing 10–30 kg (mean 18.4 (SD 5.5) kg) and 50 adults aged 18–60 yr (mean 31.8 yr) and weighing 45–89 kg (mean 64.8 (9.8) kg), ASA I or II. All

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patients were undergoing low-risk elective surgery. This study was approved by the hospital Ethics Committee and all children's guardians and adult patients gave written informed consent. We excluded any patient suffering from cardiac, vascular, respiratory, hepatic, renal, neuromuscular disorders or small joint arthritis. Patients receiving medications known or suspected to affect normal neuromuscular transmission were also excluded.

All children were premedicated with midazolam 0.5 mg kg^{-1} orally, 20–30 min before surgery. Adult patients were premedicated with diazepam 10–15 mg orally, approximately 90 min before surgery. In the operating room, an i.v. infusion of warm 5% glucose in half normal saline solution was given at a rate of 4–6 ml kg^{-1} h^{-1} via a peripheral arm vein. The ECG was monitored continuously and arterial pressure was measured every 5 min. Anaesthesia was induced with propofol 3–5 mg kg^{-1} in children and with 2–3 mg kg^{-1} in adults, and alfentanil 20 μg kg^{-1}. Tracheal intubation was performed without the use of neuromuscular blocking agents. Anaesthesia was maintained with 70% nitrous oxide in oxygen and an age-adjusted end-tidal isoflurane concentration of 1 MAC, excluding nitrous oxide (1.4–1.6% in children and 1–1.2% in adults).[9] Incremental doses of alfentanil 10 μg kg^{-1} were given as required. Ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.6–5.3 kPa).

The temperature of the skin overlying the adductor pollicis muscle was monitored and maintained at 32–33 °C. Nasopharyngeal temperature in the two age groups was maintained at 36–37 °C by the use of a warming mattress. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were monitored continuously by a multiple-gas analyser (Capnomac Ultima-SVI, Datex Instrumentarium Corporation, Helsinki, Finland). The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz repeated every 15 s. An acceleration piezo-electric transducer (Biometer International, Odense, Denmark) was fastened to the volar surface of the distal phalanx of the thumb contralateral to the site of i.v. fluid infusion. For both children and adults, the arm was immobilized in a splint and free movement during evoked thumb adduction was ensured by fixation of the extended four ulnar fingers by an elastic bandage or adhesive tape. Registration of evoked thumb acceleration, in response to adductor pollicis contractions, was carried out using a TOF Guard neuromuscular monitor (Biometer International, Odense, Denmark). After stabilization of the evoked TOF responses, each patient in the two age groups received a single i.v. bolus of rocuronium 0.6 mg kg^{-1}.

The onset time of rocuronium-induced neuromuscular block, the time interval between the end of injection of rocuronium and the development of maximum block, and the time required for spontaneous recovery of the first twitch in the TOF response (T1) to a value of 10% of its control (T0), were determined for all patients. Neostigmine antagonism was induced at T1/T0 of 10%. Patients in the two age groups were allocated randomly using closed envelopes to one of five equal dose blocks ($n=8$ for children and $n=10$ for adults). Patients in each age group received either no antagonist (control) or one of four doses of neostigmine (5, 10, 20 or 50 μg kg^{-1}). Atropine 5–20 μg kg^{-1} was given as appropriate. No other antagonist was given for the next 10 min and the end-tidal isoflurane concentration was not altered. First twitch height and TOF ratios (fractional height of the evoked fourth twitch in the TOF response in relation to the first twitch height T4/T1) were then recorded continuously for 10 min in the control and after the different doses of neostigmine. Additional doses of neostigmine and atropine were given if a TOF ratio of 80% was not achieved at the end of the 10-min period. All information derived from the acceleration transducer was recorded on a memory card and subsequently a computer printout was obtained using TOF Guard Reader software (Biometer International, Odense, Denmark).

Dose–response curves were constructed using log dose *vs* probit transformation of antagonist-assisted recovery of TOF ratios. Antagonist-assisted recovery was defined as total recovery minus spontaneous recovery that would have taken place in the absence of neostigmine. This was calculated by subtracting from the total recovery of the TOF ratio mean spontaneous recovery observed in patients who did not receive neostigmine. The result was expressed as a percentage of the maximum possible antagonist-assisted recovery, which is equal to 100% minus percentage mean spontaneous recovery.[6 7] Linear regression analyses of the dose–response curves were used to calculate the effective doses of neostigmine required to achieve 50% and 80% recovery of the TOF ratio (ED_{50} and ED_{80}, respectively), every minute for 10 min after initial administration of neostigmine. Regression lines were compared using analysis of covariance. First we tested the lines to determine if they deviated from parallelism; if they did not, the F test was applied to determine if the elevations were different. If so, Newman–Keuls multiple comparison test was applied to determine which line differed in elevation.[10] Unpaired t test was used to compare the two age groups with respect to: overall onset times, times to 10% recovery of T1/T0, T1 and TOF ratio at 5 and 10 min in the control and after different doses of neostigmine. For each age group, Dunnett's test was used to compare the degree of recovery of T1 and TOF ratio recorded at 5 and 10 min after different doses of neostigmine to the corresponding values recorded in the control group.[10] Unless otherwise specified, all results are expressed as mean (95% confidence intervals) and were considered statistically significant when $P<0.05$. Most of the statistical analyses were performed using SPSS 6.0 statistical package for Windows.

Results

All patients in the two age groups developed 100% neuromuscular block in response to the bolus doses

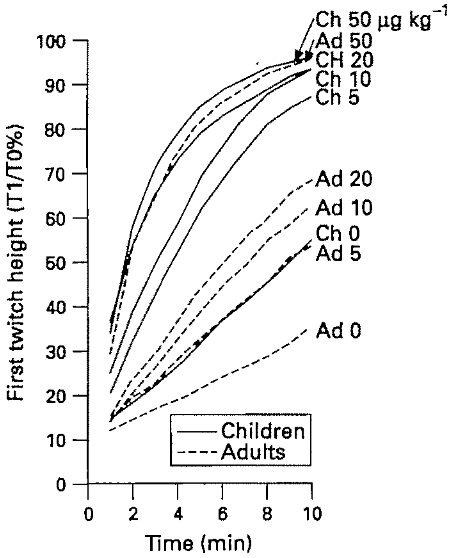

Figure 1 Mean total recovery of the first twitch height *vs* time after administration of various doses of neostigmine to antagonize 90% rocuronium-induced neuromuscular block in children (Ch) and adults (Ad). Error bars were omitted for the sake of clarity.

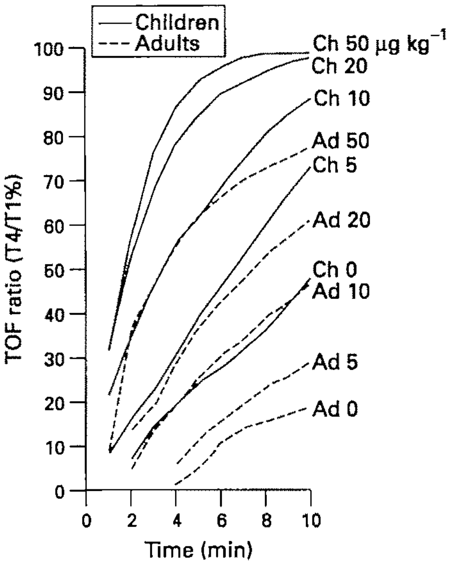

Figure 2 Mean total recovery of the train of four (TOF) ratio (T4/T1%) *vs* time after administration of various doses of neostigmine to antagonize 90% rocuronium-induced neuromuscular block in children (Ch) and adults (Ad). Error bars were omitted for the sake of clarity.

of rocuronium. The overall onset time of rocuronium-induced neuromuscular block in children was faster than that in adults (64.6 (57.7–71.5) s *vs* 83.7 (70.7–96.6) s; $P<0.05$). The time required for 10% spontaneous recovery of T1/T0 after rocuronium was shorter in children than in adults (25.4 (22.9–27.9) min *vs* 38.8 (36.1–41.4) min; $P<0.001$).

At the end of surgery, first twitch height always recovered to baseline in the two age groups. Spontaneous and antagonist-assisted recovery were more rapid in children than in adults. The courses of T1 and total recovery of the TOF ratio over the 10-min period in the control and after different doses of neostigmine in children and adults are shown in figures 1 and 2, respectively. Doses of neostigmine in the range 10–50 μg kg⁻¹ resulted in more than 90% recovery of T1 and adequate total recovery of the TOF ratio (80% or more) by the end of the 10-min period in children (table 1). A level of 80% TOF ratio was achieved in children at 4, 5 and 8 min after initial administration of neostigmine 50,

Table 1 Total recovery of the first twitch in the train-of-four (T1) in relation to control (T0) and train-of-four (TOF) ratio, spontaneously and after different doses of neostigmine in children and adults. Values are mean (95% confidence intervals). *Significantly different from the same dose of neostigmine in adults; †significantly different from control in the same age group

	T1/T0%		TOF ratio (T4/T1%)	
	5 min	10 min	5 min	10 min
Children (n=8 each)				
Control 0 μg kg⁻¹	31.7 (24.1–39.2)*	55.1 (41.5–68.7)*	24.3 (19.9–28.6)*	48.0 (39.0–57.9)*
Neostigmine 5 μg kg⁻¹	61.6 (46.9–76.2)*†	87.3 (76.1–98.6)*†	39.1 (17.1–61.1)*	73.0 (54.8–91.9)*†
Neostigmine 10 μg kg⁻¹	68.8 (63.8–73.9)*†	93.7 (88.7–98.7)*†	61.7 (50.5–72.9)*†	88.5 (81.7–95.2)*†
Neostigmine 20 μg kg⁻¹	79.0 (70.1–87.8)*†	93.7 (89.7–97.7)*†	84.6 (73.6–95.6)*†	97.7 (94.9–99.0)*†
Neostigmine 50 μg kg⁻¹	85.1 (79.5–90.7)†	96.1 (92.0–99.0)†	92.5 (85.8–99.0)*†	98.7 (96.1–99.9)*†
Adults (n=10 each)				
Control 0 μg kg⁻¹	21.6 (17.9–25.3)	35.0 (26.7–45.2)	51 (00.0–11.0)	18.7 (07.3–29.9)
Neostigmine 5 μg kg⁻¹	32.5 (26.4–38.5)†	54.2 (42.1–65.2)†	11.5 (07.5–18.4)	29.1 (22.8–35.7)
Neostigmine 10 μg kg⁻¹	39.2 (33.4–45.0)†	63.2 (52.5–73.0)†	25.6 (21.3–31.2)†	47.2 (39.1–56.4)†
Neostigmine 20 μg kg⁻¹	44.1 (38.7–48.2)†	68.7 (61.7–74.1)†	37.9 (28.1–47.6)†	61.7 (51.1–71.0)†
Neostigmine 50 μg kg⁻¹	81.6 (75.9–90.7)†	95.8 (94.0–98.3)†	61.8 (50.8–71.1)†	77.6 (67.3–83.6)†

Table 2 Effective doses of neostigmine required for 50% (ED_{50}) and 80% (ED_{80}) antagonist-assisted recovery of the train-of-four ratio in children and adults. Values are mean (95% confidence intervals)

Time after initial injection of neostigmine	Children	Adults	*P*
5 min			
ED_{50} (μg kg⁻¹)	9.86 (7.6–12.8)	34.38 (24.0–42.5)	<0.001
ED_{80} (μg kg⁻¹)	17.51 (13.4–22.9)	101.23 (81.5–126.5)	<0.001
10 min			
ED_{50} (μg kg⁻¹)	4.17 (3.0–5.7)	21.30 (17.2–26.8)	<0.001
ED_{80} (μg kg⁻¹)	7.10 (5.2–9.8)	56.56 (45.5–71.9)	<0.001

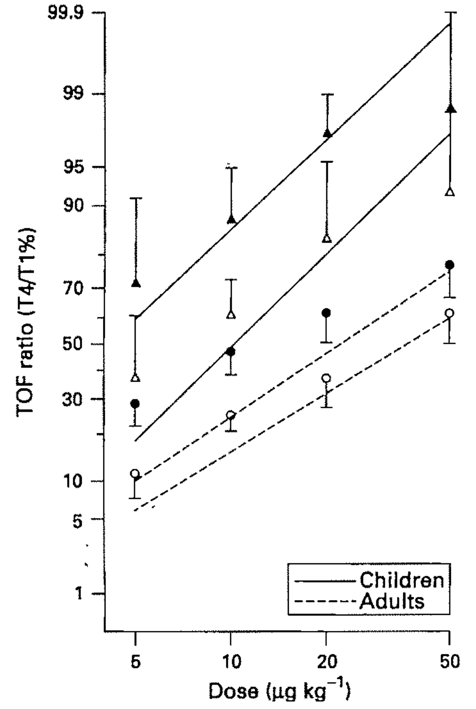

Figure 3 Dose–response curves of train-of-four (TOF) ratio recovery (probit scale) constructed at 5 and 10 min (▲, △= children and ●, ○=adults) *vs* dose of neostigmine (log scale) during antagonism of 90% rocuronium-induced neuromuscular block. Individual points represent mean values of antagonist-assisted TOF ratios attained with each dose of neostigmine. Error bars represent 95% confidence intervals.

20 and 10 μg kg^{-1}, respectively (fig. 2). In contrast, only the highest dose of neostigmine (50 μg kg^{-1}) resulted in substantial recovery of T1 to reach a value of 95.8 (94.0–98.3) % after 10 min in adults. However, adequate total recovery of 80% TOF ratio was not achieved with any of the four doses of neostigmine in adults within the same time interval (table 1, fig. 2). It is interesting to note that with respect to TOF recovery, neostigmine 5 μg kg^{-1} in children was as effective as 50 μg kg^{-1} in adults after 10 min (table 1, fig. 2).

The dose–response curves for antagonist-assisted TOF ratio recovery at 5 and 10 min were parallel in the two age groups (fig. 3). For each group, the lines constructed at 10 min were shifted significantly to the left from those constructed at 5 min ($P<0.001$ in children and $P<0.05$ in adults). The dose–response curves for children were shifted significantly to the left compared with those for adults ($P<0.001$). The effective doses of neostigmine required to achieve 50% (ED_{50}) and 80% (ED_{80}) antagonist-assisted recovery of the TOF ratios at 10 and 5 min were significantly lower in children compared with adults (table 2). The values for ED_{50}, ED_{80} in children and ED_{50} in adults are expressed as a function of time in figure 4. The ED_{50} values for adults were consistently higher than the ED_{50} and ED_{80} values in children.

Discussion

Antagonism of non-depolarizing neuromuscular block may depend on several factors including: type and dose of anticholinesterase,[6 7 11] degree of block at the time of antagonism,[12–15] anaesthetic technique used,[16] rate of spontaneous recovery and type of neuromuscular blocking drug.[6 17 18] In this study, most of these factors were standardized for the two age groups. The anaesthetic and neuromuscular monitoring techniques were similar and equal doses of neostigmine were used to antagonize 90% neuromuscular block after single standard intubating doses of rocuronium. Despite these apparent similarities, children had a more rapid onset and a shorter duration of rocuronium-induced neuromuscular block. A more rapid rate of recovery was also produced with substantially lower doses of neostigmine in children compared with adults. These age-related differences in response to rocuronium-induced neuromuscular block and its antagonism with neostigmine may have a kinetic or dynamic basis, or both.

Fisher and colleagues[2] demonstrated that the steady state volume of distribution for neostigmine in infants and children is not different from that in adults. However, infants and children have shorter elimination half-lives for neostigmine and more rapid clearance rates than adults. Therefore, the age-related differences in the rate of recovery and antagonist requirements do not seem to have a neostigmine-related kinetic basis.[19] Local differences at the neuromuscular junction such as acetylcholine reserves, acetylcholinesterase enzyme activity or the quantity of receptors at the neuromuscular junction have been suggested as possible contributing factors for the lower dose requirements of anticholinesterases in paediatric patients.[20] In contrast,

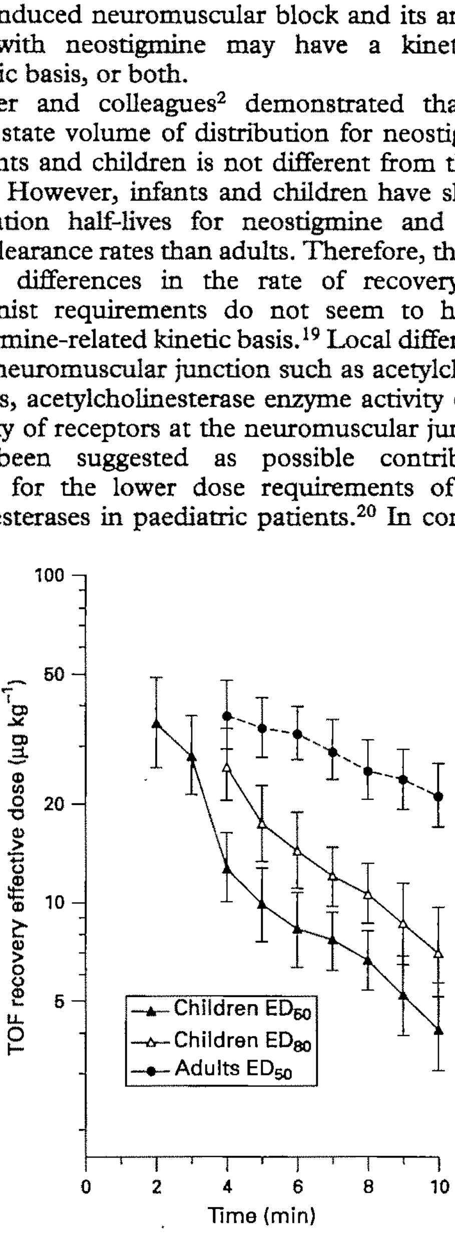

Figure 4 Effective doses for 50% (ED_{50}) and 80% (ED_{80}) antagonist-assisted train-of-four (TOF) ratio recovery *vs* time for neostigmine antagonism of 90% rocuronium-induced neuromuscular block in children and adults. Error bars represent 95% confidence intervals. Time 0=time of administration of neostigmine. The ED_{80} values for adults are not presented because they fell outside the range of the doses tested and were too high to be of clinical relevance.

it is well known that there are age-related pharmacodynamic and pharmacokinetic differences in the response to non-depolarizing neuromuscular blockers.[1 21–23] The more rapid circulation time and increased cardiac output in children are expected to expedite drug delivery to the neuromuscular junction and its removal.[23–25] Clinically, this results in acceleration of onset of neuromuscular block, more rapid rate of spontaneous recovery and reduction in duration of block in children. This was confirmed with the use of rocuronium in this and other studies.[26] In common with other neuromuscular blocking drugs, children have a shorter elimination half-life for rocuronium.[27] Smith, Donati and Bevan[6] suggested that the use of intermediate-acting neuromuscular blocking agents is associated with rapid reductions in their concentrations at the biophase. This implies that, with time, fewer receptors are occupied by the neuromuscular blocking drug with a consequent improvement in both total and antagonist-assisted recovery. This was probably the case in this study, as the effective doses of neostigmine were reduced progressively with time (fig. 4). Therefore, it appears more likely that the more rapid rate of spontaneous recovery from the effects of rocuronium-induced neuromuscular block was the predominant mechanism to explain the reduced neostigmine dose requirements and the more complete recovery observed in children.

Our results are in agreement with previously reported trends for antagonism of long-acting neuromuscular blockers, tubocurarine, pancuronium and doxacurium, in the two age groups.[2 3] However, the effective doses of neostigmine required for adequate TOF recovery were reduced considerably when rocuronium rather than longer-acting neuromuscular blockers were used.[3] Differences between the effectiveness of neostigmine antagonism of long- and intermediate-acting neuromuscular blockers have been recognized previously in adults and were attributed to different rates of spontaneous recovery.[28 29]

Rocuronium has a relatively longer duration of action than mivacurium in both adults[30 31] and children.[27 32] Therefore, at a comparable degree of neuromuscular block, anticholinesterases are expected to be more effective in antagonizing the effects of the latter.[29] However, Bevan and colleagues[4] reported recently that 10 min after administration of neostigmine 0, 5, 10, 20 and 50 μg kg^{-1} to antagonize approximately 90% mivacurium-induced block in children during nitrous oxide–propofol–fentanyl anaesthesia, the TOF ratio had recovered to mean 83.7 (SD 5.2) %, 79.3 (6.9) %, 92.8 (8.1) %, 92.2 (6.3) % and 97.0 (2.7)%, respectively. Our corresponding mean values for neostigmine antagonism of rocuronium in children were: 48.0 (95% confidence intervals 39.0–57.9) %, 73.0 (54.8–91.9) %, 88.5 (81.7–95.2) %, 97.7 (94.9–99.0) % and 98.7 (96.1–99.9) %, respectively. It is clear that when no antagonist was given, spontaneous recovery was more pronounced during recovery from mivacurium- than rocuronium-induced neuromuscular block. Therefore, the presence of comparable degrees of antagonist-assisted recovery may reflect a more effective neostigmine antagonism of rocuronium than mivacurium-induced neuromuscular block in children. This finding may appear surprising, however, factors other than anticholinesterase activity at the acetylcholine receptor level may be considered in the return of neuromuscular activity after administration of neostigmine. Szenohradszky and colleagues[33] reported recently that neostigmine was less effective in antagonizing the neuromuscular effects of mivacurium than vecuronium when administered during a continuous infusion of each blocker. In the same study, administration of neostigmine was associated with increased plasma concentrations of mivacurium. The authors suggested that the neostigmine-induced increase in mivacurium plasma concentrations may be responsible for the less effective antagonism compared with vecuronium. Neostigmine is a potent inhibitor of the butrylcholinesterse enzyme which is important for spontaneous recovery from mivacurium-induced neuromuscular block.[34 35]

In this study, inhalation of isoflurane was continued during the reversal process to ensure adequate depth of anaesthesia and prevent accidental patient movement in response to surgery, peripheral nerve stimulation, or both. This may be partly responsible for the increased dose requirements of neostigmine in adults. Other investigators have also reported that neostigmine doses in the range 40–50 μg kg^{-1} were required for adequate antagonism of 90% neuromuscular block induced by other intermediate-acting neuromuscular blockers during enflurane anaesthesia in adults.[36 37] Maintenance of anaesthesia with enflurane or isoflurane has been reported to impede the reversal process.[16] In clinical practice, however, inhalation anaesthetics are usually discontinued at the time of antagonism. This has been shown to reduce but not eliminate impairment of the reversal process.[38]

References

1. Cook DR. Muscle relaxants in infants and children. *Anesthesia and Analgesia* 1981; 60: 335–343.
2. Fisher DM, Cronnelly R, Miller RD, Sharma M. The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983; 59: 220–225.
3. Bevan JC, Purday JP, Reimer EJ, Bevan DR. Reversal of doxacurium and pancuronium neuromuscular blockade with neostigmine in children. *Canadian Journal of Anaesthesia* 1994; 41: 1074–1080.
4. Bevan JC, Tousignant C, Stephenson C, Blackman L, Reimer E, Smith MF, Bevan DR. Dose responses for neostigmine and edrophonium as antagonists of mivacurium in adults and children. *Anesthesiology* 1996; 84: 354–361.
5. Bevan DR, Kahwaji R, Ansermino J, Reimer E, Smith M, O'Connor G, Bevan JC. Residual block after mivacurium with or without edrophonium reversal in adults and children. *Anesthesiology* 1996; 84: 362–367.
6. Smith CE, Donati F, Bevan DR. Dose–response relationships for edrophonium and neostigmine as antagonists of atracurium and vecuronium neuromuscular blockade. *Anesthesiology* 1989; 71: 37–43.
7. Naguib M, Abdulatif M, Al-Ghamdi A. Dose–response relationships for edrophonium and neostigmine antagonism of rocuronium bromide (Org 9426)-induced neuromuscular blockade. *Anesthesiology* 1993; 79: 739–745.
8. Debaene B, Meistelman C, d'Hollander A. Recovery from vecuronium neuromuscular blockade following neostigmine administration in infants, children, and adults during halothane anesthesia. *Anesthesiology* 1989; 71: 840–844.

9. Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children. *Anesthesia and Analgesia* 1984; **63**: 418–420.
10. Zar J H. *Biostatistical Analysis*. Englewood Cliffs, NJ: Prentice-Hall, 1974; 151–162.
11. Naguib M, Abdulatif M. Dose–response relationships for edrophonium and neostigmine antagonism of pipecuronium-induced neuromuscular block. *Anesthesia and Analgesia* 1994; **78**: 306–311.
12. Beemar GH, Bjorksten AR, Dawson PJ, Dawson RJ, Heenan PJ, Robertson BA. Determinants of the reversal time of competitive neuromuscular block by anticholinesterases. *British Journal of Anaesthesia* 1991; **66**: 469–475.
13. Rupp SM, McChristian JW, Miller RD, Toboada JA, Cronnelly R. Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium or vecuronium. *Anesthesiology* 1986; **64**: 711–717.
14. Hennart D, d'Hollander A, Plasman C, DeJonckheere M. Importance of the level of paralysis recovery for a rapid antagonism of atracurium neuromuscular blockade with moderate doses of edrophonium. *Anesthesiology* 1986; **64**: 384–387.
15. Meistelman C, Debaene B, d'Hollander A, Donati F, Saint-Maurice C. Importance of the level of paralysis for a rapid antagonism of vecuronium with neostigmine in children during halothane anesthesia. *Anesthesiology* 1988; **68**: 97–99.
16. Dernovoi B, Agoston S, Barvais L, Baurain M, Lefebvre R, d'Hollander A. Neostigmine antagonism of vecuronium paralysis during fentanyl, halothane, isoflurane and enflurane anesthesia. *Anesthesiology* 1987; **66**: 698–701.
17. Donati F, McCarrol SM, Antazaka C, McCready D, Bevan DR. Dose–response curves for edrophonium, neostigmine, and pyridostigmine after pancuronium and d-tubocurarine. *Anesthesiology* 1987; **66**: 471–476.
18. Koscielniak-Nielsen ZJ, Law-Min JC, Donati F, Bevan DR, Clement P, Wise R. Dose–response relations of doxacurium and its reversal with neostigmine in young adults and healthy elderly patients. *Anesthesia and Analgesia* 1992; 74: 845–850.
19. Cronnelly R. Kinetics of anticholinesterases. *Clinics in Anesthesiology* 1985; **3**: 315–328.
20. Crumrine RS, Yodlowski EH. Assessment of neuromuscular functions in infants. *Anesthesiology* 1981; **54**: 29–32.
21. Fisher DM, O'Keefe C, Stanski DR, Cronnelly R, Miller RD, Gregory GA. Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. *Anesthesiology* 1982; **57**: 203–208.
22. Bush GH. Use of neuromuscular blockers in pediatric surgery and intensive care. *Clinics in Anesthesiology* 1985; **3**: 405–420.
23. Head-Rapson AG, Hunter JM. Muscle relaxants in the extremes of age. *Clinics in Anesthesiology* 1994; **8**: 501–522.
24. Donati F. Onset of action of relaxants. *Canadian Journal of Anaesthesia* 1988; **35**: S52–S58.
25. Bevan JC, Donati F, Bevan DR. Attempted acceleration of the onset of action of pancuronium: effects of divided doses in infants and children. *British Journal of Anaesthesia* 1985; **57**: 1204–1208.
26. Woelfel SK, Brandom BW, Cook RD, Sarner JB. Effects of bolus administration of Org-9426 in children during nitrous oxide–halothane anesthesia. *Anesthesiology* 1992; **76**: 939–942.
27. O'Kelly B, Fiset P, Meistelman C, Frossard J, Plaud B, Ecoffey C. Pharmacokinetics of rocuronium in pediatric patients during N_2O–halothane anesthesia. *Anesthesiology* 1992; **3A**: A907.
28. Gencarelli PJ, Miller RD. Antagonism of Org NC45 (vecuronium) and pancuronium neuromuscular blockade by neostigmine. *British Journal of Anaesthesia* 1982; **54**: 53–56.
29. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology* 1992; **77**: 785–805.
30. Naguib M. Neuromuscular effects of rocuronium bromide and mivacurium chloride administered alone and in combination. *Anesthesiology* 1994; **81**: 388–395.
31. Tang J, Joshi GP, White PF. Comparison of rocuronium and mivacurium to succinylcholine during outpatient laparoscopic surgery. *Anesthesia and Analgesia* 1996; **82**: 994–998.
32. Sarner JB, Brandom B, Woelfel SK, Dong M, Horn MC, Cook RC, McNulty BF, Foster VJ. Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide–halothane and nitrous oxide–narcotic anesthesia. *Anesthesia and Analgesia* 1989; **68**: 116–121.
33. Szenohradszky J, Lau M, Brown R, Sharma ML, Fisher DM. The effects of neostigmine on twitch tension and muscle relaxant concentration during infusion of mivacurium or vecuronium. *Anesthesiology* 1995; **83**: 83–87.
34. Baraka A, Wakid N, Mansour R, Haddad W. Effect of neostigmine and pyridostigmine on plasma cholinesterase activity. *British Journal of Anaesthesia* 1981; **53**: 849–852.
35. Fonseca J, Chaudhry IA, Marin F, Halliday NJ, Radvany T, Bikhazi GB, Foldes FF. Mivacurium block: spontaneous and neostigmine or edrophonium-induced recovery in children. *Anesthesia and Analgesia* 1994; **78**: S118.
36. Johnson RA, Harper NJN. Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine. *British Journal of Anaesthesia* 1989; **62**: 483–487.
37. Harper NJN, Wallace M, Hall IA. Optimum dose of neostigmine at two levels of atracurium-induced neuromuscular block. *British Journal of Anaesthesia* 1994; **72**: 82–85.
38. Gill SS, Bevan DR, Donati F. Edrophonium antagonism of atracurium during enflurane anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 300–305.

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Comparison of the effects of mivacurium on the diaphragm and geniohyoid muscles

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Summary

Although subjects often report difficulty with swallowing shortly after receiving neuromuscular blocking agents, difficulty with swallowing during recovery from neuromuscular blocking agents appears to be infrequent. We have used electromyography to compare onset and recovery at the diaphragm and geniohyoid airway muscles after an intubating dose of mivacurium (0.2 mg kg^{-1}) to determine if the geniohyoid muscles were particularly sensitive to neuromuscular blocking agents. Twelve adults undergoing elective surgery were anaesthetized with propofol and fentanyl and the trachea intubated without neuromuscular blocking agents. The left hypoglossal and right phrenic nerves were stimulated with percutaneous needle electrodes and the electromyogram recorded with surface electrodes. EMG responses were measured after a bolus dose of mivacurium 0.2 mg kg^{-1}. Recordings were also made of the mechanical response of the adductor pollicis to supramaximal ulnar nerve stimulation. There was no difference in the rate of onset of block for geniohyoid muscles and the diaphragm, but recovery to 25% and 90% of the control response was shorter at the diaphragm (median 14.5 (95% confidence limits 12.9–15.3) min and 23.8 (21.7–26) min) than at the geniohyoid muscle (19.4 (15.6–20.1) min and 29.2 (26.3–31.4) min), respectively ($P < 0.05$). When the train-of-four ratio of the mechanical response of the thumb reached 70%, the diaphragm and geniohyoid muscles had recovered completely in all patients. (*Br. J. Anaesth.* 1996; **77**: 716–719)

Key words
Neuromuscular block, mivacurium. Muscle skeletal, diaphragm. Muscle skeletal, geniohyoid.

A degree of neuromuscular block that does not affect quiet breathing may impair upper airway muscle function, interfering with airway patency and swallowing, and the responses that protect against aspiration. Clinical reports suggest that during onset of neuromuscular block, the muscles of the tongue are more sensitive to blockers, and swallowing can be affected by small doses, of the magnitude used for "priming".[1] During recovery, the tongue has a response similar to that of the hand muscles.[2] Such reports suggest that inadvertent residual block may affect the upper airway and hand muscles more markedly than the diaphragm, but few data are available which have compared the relative sensitivity of these muscles to non-depolarizing neuromuscular blocking agents.

We have compared the evoked responses of the diaphragm and geniohyoid muscles during onset and recovery from mivacurium. We hypothesized that there would be a more prolonged effect on the geniohyoid. We chose mivacurium to reduce the likelihood of large variation in recovery times between subjects.[3]

Patients and methods

After obtaining local Ethics Committee approval and informed consent, we studied 12 patients (eight men), ASA I or II, undergoing elective surgery. Patients were aged 31–62 yr and had no history of previous abnormal response to neuromuscular agents. No premedication was given. Before induction of anaesthesia, a venous blood sample was obtained for analysis of plasma pseudocholinesterase activity using butyrylthiocholine as substrate (normal values 3000–7000 iu $litre^{-1}$). Anaesthesia was induced with propofol 2.5 mg kg^{-1} and fentanyl 2 μg kg^{-1} and tracheal intubation was performed 2 min later without the use of neuromuscular blocking agents. Anaesthesia was continued with 60% nitrous oxide in oxygen and a continuous i.v. infusion of propofol 3–7 mg kg^{-1} h^{-1} supplemented by bolus doses of fentanyl 1 μg kg^{-1} every 30 min. Ventilation was controlled to maintain an end-tidal carbon dioxide concentration of 3.5–4.5%. The patient was placed supine with the head fixed firmly in a neutral position, and covered with a warm air heating blanket (Bair Hugger, Augustine, La Praye, Switzerland).

The right phrenic nerve was stimulated using percutaneous insulated needle electrodes (Xomed, Jacksonville, FL, USA) inserted at the inferolateral

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edge of the sternomastoid muscle, 1.5–3.5 cm deep. The electrode was inserted anterior to the scalene muscles at the level of the cricoid cartilage and directed inferiorly, anteriorly and medially. Satisfactory stimulation of the nerve caused a hiccuping movement of the right hemidiaphragm, with no activity of muscles supplied by the brachial plexus. The electrode was fixed in position with adhesive tape. The activity of the diaphragm was measured by placing two silver–silver chloride surface electrodes, 2 cm apart, in either the seventh or eighth intercostal space between the right anterior axillary and midclavicular lines where the response was maximal.

The left hypoglossal nerve was stimulated with the same type of percutaneous electrodes placed to a depth of approximately 1 cm under the angle of the mandible and directed anteriorly.[2] The activity of the geniohyoid muscles was measured with surface electrodes, placed 2 cm apart, midway between the mentum and the hyoid bone, between 0.5 and 1.5 cm lateral to the midline on the same side as the stimulating electrodes. Supramaximal stimuli (20–35 mA) were applied at 0.1 Hz and the rate of mechanical ventilation was adjusted so that the stimuli occurred at the end of expiration.

The activity of the muscles was amplified and recorded with a gated EMG amplifier using a latency of 2 ms and a window of 10 ms (Viking 2, Nicolet Instruments, Trappes, France). We measured the peak-to-peak amplitude of the compound action potential.

The left ulnar nerve was stimulated supramaximally at the wrist with surface electrodes using train-of-four (TOF) stimulation every 12 s. The force of contraction of the adductor pollicis was measured with a force transducer (Entran, Clayes sous Bois, France).

After steady responses for each muscle had been present and recorded for 3 min, a single dose of mivacurium 0.2 mg kg^{-1} was given i.v. over 10 s and the evoked EMG responses and force of contraction of the thumb recorded until full recovery. The times to 90% and maximum effect during onset, and to 5, 10, 25, 50, 75 and 90% of the control response during recovery were measured for all muscles. We calculated the recovery index as the time taken to recover 25–75% of the evoked response. We noted the time that the thumb TOF ratio (fourth to first response) became 70%.

Onset and recovery times were compared between the geniohyoid and diaphragm muscles with the Wilcoxon rank sum test, using the SIPHAR statistical program (Simed, Creteil, France). $P < 0.05$ was considered significant. Times are reported as median (95% confidence intervals).

Results

Mean age of the patients was 50 (range 31–72) yr and mean weight 70 (SD 12) kg. Plasma pseudocholinesterase activities were within the normal range, with a mean value of 4390 (SD 990) iu $litre^{-1}$. There were no adverse events or clinically important changes in heart rate or arterial pressure during the study.

The times to 90% and maximal depression of response were similar for the diaphragm and geniohyoid muscles. Figure 1 shows the time course of recovery of muscle responses after mivacurium, and the times of onset and recovery are given in table 1. Recovery times for the diaphragm were significantly less than those for the geniohyoid. Recovery indices of the diaphragm and geniohyoid muscles were similar and significantly less than the values for the thumb. At 70% TOF for the thumb, the responses of the geniohyoid muscles and diaphragm had returned to control values in all subjects.

Recovery of the electromyogram signal was usually complete. At full recovery, the absolute percentage differences between the responses measured after administration of the neuromuscular blocking agent, compared with the response obtained before the drug, were 3.5 (0.8–18.8) % for the geniohyoid and 3.0 (0.5–7.1) % for the diaphragm.

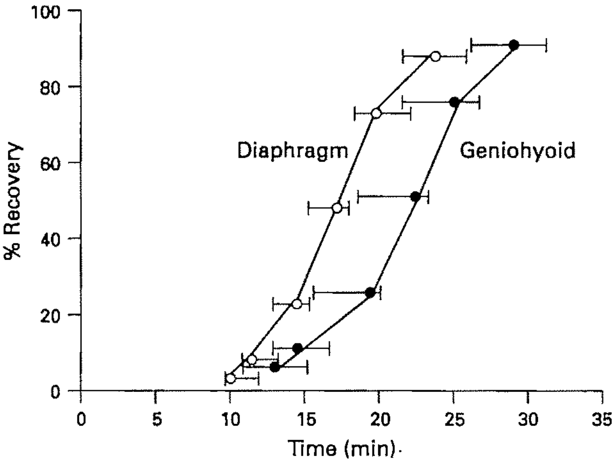

Figure 1 Time course of recovery of the geniohyoid (●) and diaphragm (○) responses after administration of mivacurium 0.2 mg kg^{-1} i.v. (median, 95% confidence intervals).

Table 1 Onset and recovery characteristics for the diaphragm, geniohyoid and adductor pollicis (median (5–95% confidence limits of the mean)). *Significant differences between diaphragm and gehiohyoid muscles (P <0.05); ††significant differences between adductor pollicis and both diaphragm and geniohyoid (P <0.01)

	Diaphragm	Geniohyoid	Adductor pollicis
Onset (90% block) (s)	130 (127–157)	122 (116–52)	155 (151–182)
Onset (max. block) (s)	158 (139–177)	161 (145–177)	192 (185–213)
Maximum depression (%)	100 (98.5–100)	100 (99–100)	100 (100–100)
Recovery (10% block) (min)	12 (11–13)	15 (13–17)*	25 (23–28)††
Recovery (50% block)	19 (15–18)	22 (18–23)*	33 (31–37)††
Recovery (90% block)	24 (22–26)	29 (26–31)*	38 (35–43)††
Recovery index (min)	6.2 (5.3–7.0)	5.75 (5.2–7.6)	9.9 (8.6–11.1)

Discussion

We used the evoked response of the EMG to measure neuromuscular block in the diaphragm and geniohyoid muscles, because estimation of the mechanical responses of these muscles is complex and invasive. When resting muscle length is constant (i.e. preload is constant) and length during contraction does not alter (i.e. the transducer used has a large elastance), neural activation of a muscle, the evoked EMG activity, and the tension developed are closely related. Under experimental conditions, diaphragmatic contraction assessed by transdiaphragmatic pressure correlated well with the EMG signal[4] and it is likely that under the conditions of this study both measurements would have yielded similar results. In some circumstances EMG assessment of neuromuscular transmission, such as we used, may not indicate true functional state of the muscle. It is necessary to separate the effects on transmission, force generation and mechanical activity (lengthening or shortening). Measurement of an evoked response to a single stimulus is not affected by factors such as fade, which may be present when the muscle is activated with natural neural frequencies. However, if both EMG and mechanical response are measured in these circumstances, these responses are likely to be equally affected by factors that affect transmission, such as fade. Factors that alter muscle contractility or coordination may adversely affect airway protection and stability, even when neuromuscular transmission is satisfactory, and neuromuscular transmission has also to be assessed at physiological frequencies to be certain that this is so.[5]

We studied the geniohyoid muscle with EMG surface electrodes, and it is possible that activity from other facial muscles could have caused interference. However, because unilateral selective stimulation of a hypoglossal nerve is unlikely to cause significant activation of other muscles, and the position of the recording electrodes was close to the muscles studied, we are confident that the method allowed specific assessment of the mylohyoid–geniohyoid muscle complex. These muscles act to maintain airway patency[6] and are involved in the initial phase of swallowing. Impairment of neuromuscular transmission of these muscles can impair pressure generation during swallowing[7] but the timing of muscle activation does not appear to be reduced, indicating that coordination is less affected.

The dose of mivacurium chosen caused complete paralysis of the diaphragm in 11 of 12 subjects, despite resistance of this muscle to the action of non-depolarizing neuromuscular blocking agents. As the dose chosen was 2.5–3 times the ED_{95} for the thumb,[3] when given during nitrous oxide–opioid anaesthesia, it is not surprising that it caused rapid and almost complete paralysis of the diaphragm.

With this large dose, the onset of action at the geniohyoid muscles and diaphragm was similar, probably reflecting similar kinetic factors, such as muscle blood flow.[8] The onset of facial and diaphragm paralysis are similar and measurement of orbicularis oculi responses has been suggested as a good index of the time necessary for intubation.[9] In this study, loss of transmission for both the geniohyoid and diaphragm occurred at the same time, reinforcing the value of facial paralysis as a marker of adequate relaxation for intubation, which requires good relaxation of both diaphragm and pharyngeal muscles. Onset of neuromuscular block at the arm takes longer, indicating a smaller blood flow to the arm than to the diaphragm.[10]

Although during onset of action the importance of kinetic factors is great, during recovery the relative potencies of blockers at the two sites becomes more relevant as blood and tissue concentrations decrease progressively and in parallel.[11] In some studies, although the dose–response relationship was not assessed formally, relative transmission during recovery has been taken as a reasonable index of relative potencies,[9] particularly for longer-acting agents. During steady state neuromuscular block and recovery, sparing of the diaphragm relative to other muscles is well described.[12] The differences between the diaphragm and geniohyoid muscles in this study showed that the diaphragm has a greater margin of safety than the geniohyoid muscles, although this difference was not marked with mivacurium.

We tested the hypothesis that the actions of the neuromuscular blocking agent, mivacurium, would differ during onset of effect and recovery from effect, and that recovery of the geniohyoid muscles would be slow and similar to that of the thumb. Previous studies performed under similar conditions have suggested that the airway muscles are much more sensitive to neuromuscular blocking agents than the diaphragm, and hence patients may be unable to overcome airway obstruction or to clear the airway of foreign material despite respiratory muscle activity adequate for ventilation alone. Isono and co-workers showed in dogs that geniohyoid block was more intense than diaphragm block during onset and recovery from the action of vecuronium.[13] In patients, the same group or investigators found that partial neuromuscular block disturbed swallowing even though ventilation was adequate.[7] However, there has been no study in humans where simultaneous recovery of the two muscle groups has been assessed using the same method.

Although we found some difference, this was less than might have been predicted. Recovery after mivacurium may be more dependent on kinetic factors than recovery from other agents. Although blood flow may not normally affect recovery with agents such as atracurium and vecuronium, it may be a more important factor in the termination of action of agents with a very short half-life, such as mivacurium, leading to a faster recovery and shorter recovery index in the geniohyoid muscles because they seem to have a large blood flow.

When the TOF ratio for the thumb was 70%, no residual depression of either the diaphragm or geniohyoid muscle was present, showing that recovery from an intubating dose of mivacurium confers a greater safety margin for the geniohyoid muscles than for atracurium and vecuronium.[2]

References

1. Mahajan RP, Laverty J. Lung function after vecuronium pretreatment in young, healthy patients. *British Journal of Anaesthesia* 1992; **69**: 318–319.
2. D'Honneur G, Guignard B, Slavov V, Ruggier R, Duvaldestin P. Comparison of the neuromuscular blocking effect of atracurium and vecuronium on the adductor pollicis and the geniohyoid muscle in humans. *Anesthesiology* 1995; **82**: 649–654.
3. Savarese JJ, Ali HH, Basta SJ. The clinical pharmacology of mivacurium chloride (BW1090U): a short acting non-depolarising ester neuromuscular blocking drug. *Anesthesiology* 1988; **68**: 723–732.
4. Lebrault C, Chauvin M, Guirimand F, Duvaldestin P. Relative potency of vecuronium on the diaphragm and the adductor pollicis. *British Journal of Anaesthesia* 1989; **63**: 389–392.
5. Gerber HR, Johansen SH, Mortimer JT, Yodlowski E. Frequency sweep electromyogram and voluntary effort in volunteers after d-tubocurarine. *Anesthesiology* 1977; **46**: 35–39.
6. Roberts JL, Reed WR, Thach BT. Pharyngeal airway-stabilizing function of sternohyoid and sternothyroid muscles in the rabbit. *Journal of Applied Physiology* 1984; **57**: 1790–1795.
7. Isono S, Ide T, Kochi T, Mizuguchi T, Nishino T. Effects of partial paralysis on the swallowing reflex in conscious humans. *Anesthesiology* 1991; **75**: 980–984.
8. Nigrovic V, Banoub M. Onset of the nondepolarizing neuromuscular block in humans: quantitative aspects. *Anesthesia and Analgesia* 1993; **76**: 85–91.
9. Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi and adductor pollicis muscles. *Anesthesiology* 1990; **73**: 870–875.
10. Goat VA, Yeung ML, Blakeney C, Feldman SA. The effect of blood flow on the activity of gallamine triethiodide. *British Journal of Anaesthesia* 1976; **48**: 69–73.
11. Ham J, Miller RD, Sheiner LB, Matteo RS. Dosage schedule independence of d-tubocurarine pharmacokinetics and pharmacodynamics, and recovery of neuromuscular functions. *Anesthesiology* 1979; **50**: 528–533.
12. Lee CH. Some characteristics of neuromuscular block in the respiratory musculature in anaesthetized man. *Canadian Anaesthetists Society Journal* 1976; **23**: 125–134.
13. Isono S, Kochi T, Ide T, Sugimori K, Mizuguchi T, Nishino T. Differential effects of vecuronium on diaphragm and geniohyoid muscle in anaesthetized dogs. *British Journal of Anaesthesia* 1992; **68**: 239–243.

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Concentration-related effects of propofol on the auditory evoked response

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Summary

We have studied the effects of propofol, as the sole agent, at blood concentrations of 1–10 μg ml^{-1}, on the first 100 ms of the auditory evoked response (AER) in 41 women before gynaecological surgery. AER were recorded with the patients awake and then after 30 min of one of seven stepped infusion regimens. Each patient was studied at only one blood concentration. The recordings were edited and processed off-line by coherent signal averaging, to obtain reliable estimates of each AER. We measured standard features, such as amplitudes and latencies of brainstem wave V and the mid-latency waves Na, Pa and Nb. In addition, we studied several composite indices, intended to give a more global characterization of the AER. We derived relationships between the doses and blood concentrations of propofol, features of the AER and response to eyelash stimulus and venepuncture. Nb latency was better than either concentration or dose rate of propofol in providing a confident explanation of the likelihood of eyelash response (which parallels the response to command). A cut-off value of 53 ms had a sensitivity of 100%, a specificity of 96% and an overall correctness of 98% as a discriminator of eyelash response *vs* no response. Several alternative AER-derived indices provided more than 90% correctness in discrimination, as did a dose rate of propofol of 6.3–7.8 mg kg^{-1} h^{-1} or a blood concentration of 2.9 μg ml^{-1}. We conclude that the concentration and dose of propofol were good discriminators of response to venepuncture, while the latency of the Na wave was the most successful of the AER features. (*Br. J. Anaesth.* 1996; **77**: 720–726)

Key words
Anaesthetics i.v., propofol. Brain, electroencephalography. Monitoring, evoked potentials. Monitoring, electroencephalography.

Graded changes in the auditory evoked response (AER) occur as concentrations of anaesthetic agents are altered, mainly in the mid-latency waves (15–80 ms).[1] Brainstem components are said to be unchanged by anaesthetics, while later components (>80 ms) are probably too affected by mental activity[2 3] to allow the effects of anaesthetics to be discerned accurately. Several workers have tried to demonstrate loss of implicit/explicit memory during anaesthesia, correlating it with the AER, but results so far are inconclusive.[4 5]

Previous studies of AER during anaesthesia have included the effects of several drugs in combination[6–9] and have been limited to small numbers of patients (i.e. 6–10 patients) or short exposure times that may not have allowed steady states to be established in brain or blood. Forrest and colleagues[10] found that the changes in the electroencephalogram (EEG) were unstable during the first 10–15 min of a targeted propofol infusion regimen. Only after 20 min did a steady neurophysiological state emerge. In this study we used propofol as a sole agent in patients free from surgical stimulation. We attempted to determine how the shape of the transient AER varied with a range of stable blood concentrations. The responsiveness of patients to standardized stimuli was assessed. Each patient was subjected to only one concentration of propofol.

Patients and methods

With approval from the local research Ethics Committee and written informed consent, we studied 41 healthy women, ASA I or II, median age 40 (range 25–71) yr. The patients were undergoing elective gynaecological surgery and receiving no medication other than hormone replacement therapy or oral contraceptives. We attached two sets of bipolar silver–silver chloride electrodes in a conventional configuration.[11] One set was placed on the vertex (positive) and 2 cm above the inion (negative), and the other on the vertex (positive) and the earlobe (negative), with the forehead as reference. We applied them in the ward and ensured stable impedances below 5 kΩ. In the anaesthetic room we sited an i.v. cannula and started routine clinical monitoring with ECG, non-invasive arterial pressure measurement and pulse oximetry.

We made a set of baseline AER recordings (see below) with patients awake and relaxed, with eyes lightly closed. Patients then received propofol from a

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Table 1 Infusion schemes for the seven groups of patients. Six patients were allocated to each group except for group 7 which had five patients

Group	Initial dose ($mg\ kg^{-1}$)	Infusion 1—after initial dose ($mg\ kg^{-1}\ h^{-1}$)	Infusion 2—after 10 min ($mg\ kg^{-1}\ h^{-1}$)	Infusion 3—after 20 min ($mg\ kg^{-1}\ h^{-1}$)
1	0.7	7	5.6	4.2
2	1	10.3	8.2	6.2
3	1.35	13.5	10.8	8.1
4	1.68	16.8	13.4	10.1
5	2	20	16	12
6	2.5	25	20	15
7	3	30	24	18

calibrated infusion pump (Graseby 3400 series) according to one of seven different manually controlled infusion schemes (table 1). These were intended to achieve and maintain a range of stable blood concentrations of propofol[12] between 1.0 and 10.0 $\mu g\ ml^{-1}$, with corresponding states of responsiveness between light sedation and deep unconsciousness.[13] The infusions were allocated openly and sequentially in blocks of seven (i.e. first patient to group 1, second patient to group 2, ... seventh patient to group 7, eight patient to group 1, etc.). Patients breathed spontaneously. Sedated patients received oxygen 4 litre min^{-1} through a Hudson mask. Anaesthetized patients received 40% oxygen from an entrainment T-piece via a laryngeal mask airway.

We made repeat recordings of AER at 10, 20 and 30 min after the start of the propofol infusion. Only recordings at 30 min were considered for this study. Immediately after the 30-min recordings, we recorded each patient's responses to the instruction "open your eyes", stroking an eyelash and venepuncture. We obtained venous blood samples from the contralateral arm to the infusion, which were stored in oxalate tubes for subsequent assay by high pressure liquid chromatography (HPLC).[14] This had a coefficient of variation of 7.3% at a propofol concentration of 2.0 $\mu g\ ml^{-1}$. The laboratory staff were unaware of the dose regimen. Anaesthesia for surgery was then provided by the anaesthetist covering the operating list.

AER RECORDING EQUIPMENT

We used an 80486 computer (Elonex plc, London, UK) to control two signal processing microprocessors (CED 1401 plus, Cambridge Electronic Design Ltd, Cambridge, UK), one as a flexible auditory stimulator and the other for data acquisition. The stimulator unit contained software (AUDPLUS, Cambridge Electronic Design) that allowed preprogramming of the qualitative and quantitative characteristics of the stimuli. These were delivered from a fixed-gain buffer amplifier via insert headphones at amplitudes 80 dB above the normal hearing threshold. Each set of recordings contained the responses to 500 bursts of a 2-kHz tone of 5 ms duration, followed by 500 rarefaction clicks of 0.5 ms duration.

We recorded a "sweep" of raw EEG data lasting 128 ms after each stimulus on a high quality, patient-isolated EEG amplifier (CED 1902). Its settings (gain, calibration and filtering) were controlled by the computer acquisition software. The amplifier had second-order, high-pass and low-pass filters set, respectively, to 3 dB points of 15 and 200 Hz. Data acquisition software (SIGAVG, Cambridge Electronic Design) controlled the repetition rate of the auditory stimulus (5.9 Hz), duration of "sweep" (128 ms) after each stimulus and sampling frequency of the EEG signals (1 kHz) during each sweep. Each sub-set of 500 sweeps took approximately 90 s. A monitor displayed the real-time coherent average AER and the sweeps were stored on disk for definitive off-line processing.

AER PROCESSING (OFF LINE)

Off-line processing of each sweep consisted of iterative loops of editing and coherent averaging (to obtain the most reliable estimate of the AER) followed by feature extraction from the best estimate. Editing was done semi-automatically using custom-designed signal processing software (SPIKE 2 language, Cambridge Electronic Design). Additionally, all sweeps were digitally filtered by a 15-Hz high-pass filter to remove low frequency EEG.

Editing and coherent averaging

Coherent averaging is a signal processing strategy for extracting a small response from a background of random overwhelming noise in sweeps of recorded signals after a repeated stimulus. As a running average is obtained of the values of a signal after each stimulus, the positive and negative deflections of the noise (background EEG activity, muscle activity, 50 Hz from mains, etc.) should cancel each other out. However, the consistent deflections produced by a contained response should reinforce one another ever more strongly as successive sweeps contribute to the average. This method fails if there are major incidents that rise above ordinary noise. These could distort the final AER or make it totally incorrect. Our previous unstimulated EEG studies during propofol anaesthesia[10] taught us that such incidents were liable to occur. These included movement artefacts in unanaesthetized patients, ECG spikes and spontaneous "burst" activity in patients receiving higher concentrations of propofol (fig. 1). Some patients also showed time-locked myogenic responses to auditory stimulation. Many of these incidents in the EEG have frequency contents so close to the important frequencies in the AER that it is not feasible to remove them by filtering. Editing is a reasonable alternative.

We identified these incidents by the program, producing compressed time displays of three features of the EEG during the 500 sweeps of recording: the first simply showed the maximum amplitude (used for rejecting noise spikes), the second the integral of the rectified waveform (used for rejecting high propofol concentration effects) and the third the maximum differential value of the waveform (used for rejecting ECG signals). Thresholds were determined by inspection to differentiate the normal background activity from incidental transients of unwanted data. A coherent average was then made using those sweeps that were below the chosen thresholds. The others were rejected. The quality of the resulting average was checked by examining the width of the confidence limits that contained the best estimate of the time course of the AER. The best estimate, with that edition of sweeps, was compared with the estimates produced from the first and second half of the file of edited sweeps. Its shape was also compared with that of the best estimate produced by the tone stimuli. A further test of the editing and data-processing was that the coherent average of a similarly edited batch of 500 sweeps of the contemporaneous background EEG, with no auditory stimulus, should show a flat trace. Failure to achieve a confident estimate of the AER by any of the above criteria required the cycle of editing and coherent averaging to be repeated until a satisfactory estimate was obtained. Otherwise the analysis was abandoned and the information discarded. The final satisfactory estimates of the AER were stored as separate files.

Feature extraction from the best estimates of the AER

The simple features that were extracted consisted of amplitudes (measured from the preceding peak or trough) and latencies (from the stimulus) of the peaks or troughs of the conventionally labelled components of the AER (brainstem wave V, Na, Pa, Nb). These were measured by applying cursors to the screen display of each satisfactory estimate of the AER. Several empirically devised composite measures of the complete AER wave were also recorded, including: (i) integral of the rectified waveform between 15 and 70 ms (summation index); (ii) integral of the rectified smoothed differential of the waveform between 20 and 70 ms (differential index); (iii) reciprocal of the difference between Na and Nb latencies (basic frequency index); (iv) index of the superimposability of each waveform on that of the grand average of several patients' baseline (awake) AER waveforms (amplitude, at each time, of the AER waveform under investigation was multiplied by the corresponding amplitude of the grand average, and the successive product terms were summed over the first 50 ms).

STATISTICAL ANALYSES

The groups were not randomly allocated, and therefore we used analysis of variance to examine for bias in ages, weights and baseline arterial pressures: we also examined the haemodynamic effects of the different doses of propofol, 30 min after the start of the infusions. Relationships between dose and concentration, and between concentration and the values of the features extracted from the AER, were determined by non-linear curve-fitting programs (Sigma Plot for windows 5, Jandel Scientific, Erkrath, FRG and Unistat for windows). A stepwise multiple logistic regression (LOGIST, SAS version 6, for windows. SAS institute Inc, Cary, NC, USA) was used to identify explanators of the patient's responses to eyelash and venepuncture. The conventional AER amplitudes and latencies and the composite indices were offered as potential explanators, together with the dose and concentration of propofol. The LOGIST procedure can output sensitivity, selectivity and correctness if different cut-off probabilities are used to classify responses as present or absent. Data on verbal response were not examined formally. They could be inaccurate because the insert headphones interfered unpredictably with hearing through normal channels. However, the responses achieved were virtually superimposable on the eyelash responses, as in our other studies.[10 13] A probit analysis (SAS for windows version 6, SAS Institute, Cary NC, USA) was used in addition, to estimate (with confidence limits) the values of the single and composite AER features and the doses and concentrations of propofol that corresponded to 50% and 95% probability of no response.

Results

There were no significant differences between the seven groups in age, weight or arterial pressure, either at baseline or after 30 min of infusion.

SAMPLING AND EDITING OF AER

For the period of propofol infusion, data from six

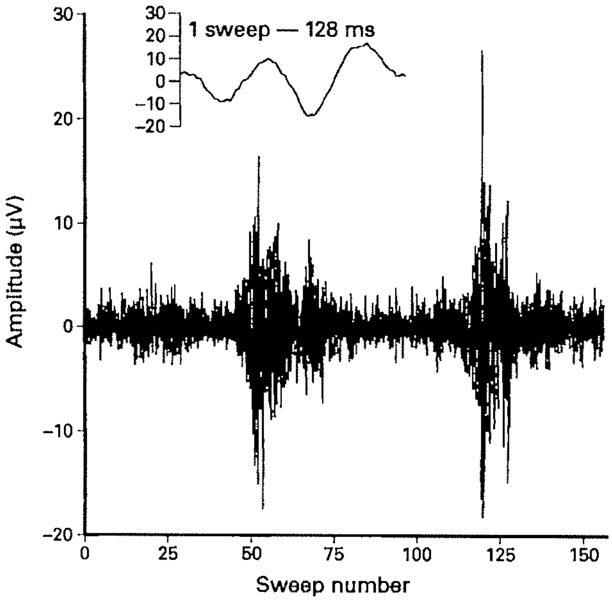

Figure 1 A compressed time display of 150 sweeps of raw data during which auditory stimuli were being given. The inset shows a single sweep (No. 52) of raw data containing both AER and EEG, with the stimulus given at the vertical axis and the sweep lasting 128 ms.

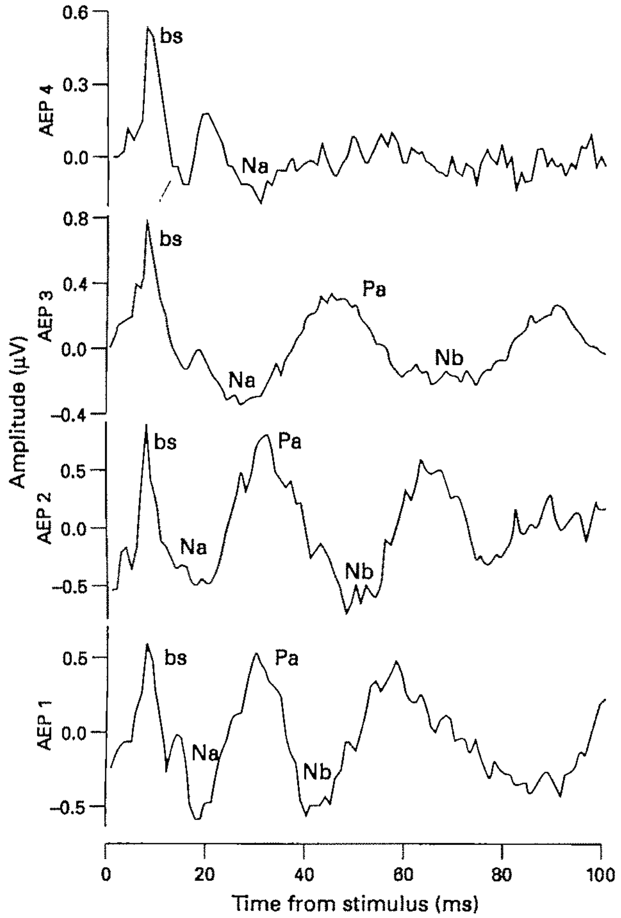

Figure 2 Example AER estimates for wakefulness (AEP 1) and at three different infusion rates of propofol, giving blood concentrations of propofol of 1.5 $\mu g\ ml^{-1}$ (AEP 2, eyelash response present), 3.8 $\mu g\ ml^{-1}$ (AEP 3, no response to eyelash or venepuncture) and 8.9 $\mu g\ ml^{-1}$ (AEP 4). Each trace has a different amplitude scale.

patients could not be included in the analysis: two coughed uncontrollably on the allocated dose of propofol (groups 3 and 4); two produced time-locked myogenic responses that overwhelmed the AER estimate; in one patient, the coherent average of the unstimulated EEG did not tend to zero; the EEG from the last patient was too heavily contaminated with artefact to provide a confident estimate of the AER. Therefore, there were 35 estimates remaining after 30 min of propofol infusion. In these 35 patients, only 16 estimates were obtained of awake AER. The estimates that were made required a variable amount of editing to exclude incidents and artefacts from the coherent average.

Figure 1 is an example of a compressed time display of the first 150 sweeps in a set of 500, and shows what can happen at the infusion rates of propofol that produce blood concentrations of more than 3 $\mu g\ ml^{-1}$. Periodic increases in amplitude are reminiscent of the spindling in burst suppression, but the increases are much greater and the contained frequencies (indicated in the insert of a single sweep) are higher, overlapping with the principal frequencies in the AER. Features similar to this appear in the presence or absence of auditory stimulation and necessitated the editing described in the methods.

Figure 2 shows four example AER from three patients, illustrating qualitatively the progression from awake (AEP 1) through to the effects of three dose rates of propofol that span the range used in this study. It shows the reduction in amplitude and delay of the mid-latency components, with relatively little effect on the brainstem response.

DOSE–CONCENTRATION EFFECTS

The relationship between dose rate and concentration of propofol was described as well by linear regression as by one with higher terms in infusion rate:

$$\text{concentration } (\mu g\ ml^{-1}) = -1.12 + 0.53 \times \text{final infusion rate } (mg\ kg^{-1}\ h^{-1})\ (r^2 = 0.83)$$

CONCENTRATION–AER EFFECTS

Figure 3 shows the relationships between propofol concentration and two of the measured features of the AER. The relationship with Na latency was almost linear, whereas that for Nb was non-linear. There was an apparent ceiling effect at approximately 70–80 ms which was reached normally at propofol concentrations greater than 6 $\mu g\ ml^{-1}$. Higher concentrations attenuated the responses to an extent that made Nb latency difficult to judge. This also occurred with four AER recorded at propofol concentrations less than 6 $\mu g\ ml^{-1}$. Data for Nb were fitted significantly better by a quadratic than by a linear equation in concentration. The

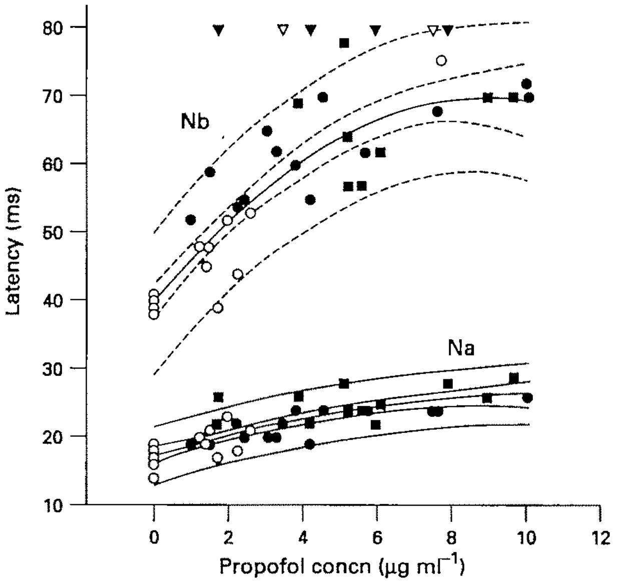

Figure 3 Relationships between Nb latency, Na latency and whole blood propofol concentration. The overlapping open circles at zero concentration represent the distributions of 13 values for Nb (mean latency 39.6 (SD 1.0) ms) and eight values for Na (mean latency 17.0 (1.5) ms) obtained from awake patients. All other values were obtained at 30 min after the start of infusion. ○=Patients responding to eyelash and venepuncture stimuli; ●=patients responding to venepuncture stimulus only; ■=patients not responding to eyelash or venepuncture; ▼=patients not responding to eyelash or venepuncture and also the AER was too suppressed to allow estimation of Nb; ▽=patients responding to venepuncture only and the AER was too suppressed to allow estimation of Nb. The 95% confidence limits for the best fit regression line and for individual data points are superimposed on each plot.

Table 2 Relationships between blood propofol concentration (conc.) and conventional and composite features of the AER, with coefficients of determination (r^2)

Variable	Equation	r^2
Nb latency	$=39.9+6.7\text{ conc.}-0.37\text{ conc.}^2$	0.83
Nb amplitude	$=1.19-0.26\text{ conc.}-0.016\text{ conc.}^2$	0.44
Pa latency	$=28.5+3.9\text{ conc.}-0.2\text{ conc.}^2$	0.79
Pa amplitude	$=1.34-0.27\text{ conc.}+0.17\text{ conc.}^2$	0.42
Na latency	$=17.4-1.66\text{ conc.}-0.07\text{ conc.}^2$	0.70
Na amplitude	$=1.27-0.11\text{ conc.}+7.32\text{ conc.}^2$	0.17
BS latency	$=6.9+0.18\text{ conc.}-0.02\text{ conc.}^2$	0.25
Frequency	$=42.2-5.79\text{ conc.}+0.40\text{ conc.}^2$	0.69
Superimposability	$=4.2-1.9\text{ conc.}+0.15\text{ conc.}^2$	0.69
Summation	$=24-3.95\text{ conc.}+0.23\text{ conc.}^2$	0.36
Differential	$=5.94-1.32\text{ conc.}+0.095\text{ conc.}^2$	0.50

relationships for the other features that were extracted are summarized in table 2 as quadratic equations in concentration.

DOSE, CONCENTRATION AND AER EFFECTS ON RESPONSIVENESS TO STIMULI

When offered all possible AER explanators together (conventional and composite features) the stepwise multiple regression process identified only Nb latency as a significant explanator of the occurrence of an eyelash response. If Nb latency was not offered, stepwise multiple logistic regression process identified several other AER features as partial alternative explanators. A similar process was carried out with propofol concentration and dose rates. In the corresponding analyses for the venepuncture response, Na latency itself gave as complete an explanation as the total set of offered AER explanators, although others also had partial explanatory effect that was overlapped by that of Nb.

Table 3 summarizes the relationships between likelihood of suppressing eyelash or venepuncture responses and the values of various AER and non-AER features. The values for 50% and 95% probability of no response were estimated by probit analysis.

The logistic regression process produces values for sensitivity, specificity and correctness in discrimination that would be obtained if different probabilities (or the corresponding value of the explanator in a single explanator regression) were to be used as cut-off points for classification of response *vs* no response. For example, an Nb latency of 53 ms had a sensitivity of 100%, a specificity of 96% and a correctness of 98% as a discriminator of eyelash response. This is confirmed in figure 3: if a horizontal line is placed at 53 ms, all eyelash responders are below it and 20 of 21 non-responders are above it. For concentration, the best discriminator, a vertical line placed at 2.9 μg ml^{-1} shows all responders to the left but only 15 of the 21 non-responders to the right. Table 4 lists the threshold values of the seven best discriminators of eyelash and venepuncture responses, ranked in order of correctness, with the associated values of sensitivity and specificity in discriminating responders from non-responders.

Table 3 Estimated values (95% confidence limits) of a selection of AER and non-AER explanators that are required to have 50% or 95% probability of suppressing the eyelash or venepuncture response in the sample. Dose=final infusion rate of propofol, concentration=blood propofol concentration

Variable	50% probability of no response	95% probability of no response
Eyelash:		
BS latency (ms)	7 (6.6–7.5)	8.2 (7.7–14)
Na latency (ms)	20 (16–23)	24 (22–48)
Nb latency (ms)	52 (46–56)	60 (56–79)
Frequency (Hz)	32 (29–39)	28 (16–31)
Concentration μg ml^{-1}	1.9 (1.4–2.7)	3.3 (2.5–5.5)
Dose (mg kg^{-1} h^{-1})	5.8 (4–7.5)	8.2 (6.9–15.6)
Venepuncture:		
BS latency (ms)	7.8 (7.4–8.7)	9 (8.3–12.3)
Na latency (ms)	24 (23–26)	29 (26–37)
Nb latency (ms)	67 (62–75)	85 (76–122)
Frequency (Hz)	23 (17–27)	14 (2–18)
Concentration (μg ml^{-1})	6.5 (4.4–12.7)	13 (9–32)
Dose (mg kg^{-1} h^{-1})	13.2 (10.6–18)	23 (18–37)

Discussion

The conditions of the study were not typical of clinical anaesthesia, but the design allowed examination of the effects of propofol as a sole agent, without the confounding effects of surgery. The relationship between the infused dose rate and 30-min propofol concentrations was consistent with that found in our previous study on unstimulated EEG[10] which also indicated that 30 min was the minimum time needed for the stepped infusions to produce a stable neurophysiological state.

Great care was needed to obtain confident estimates of the AER. Awake, unpremedicated patients were often tense, despite all efforts to relax them. More than 50% of their AER were contaminated by time-locked muscle responses, such as the post-auricular response. The remaining reliable awake AER had a fairly consistent waveform which was also similar to many awake AER recorded in subsidiary studies on volunteers. Much of the contamination (including, in all patients, the post-auricular response) disappeared during infusion of propofol, but could be replaced by other activities, such as in figure 1, for which careful empirical analysis seemed the only solution. For applications of AER recording to on-line feedback of anaesthetic depth, methods of automating the editing process are needed, unless the contaminating activity can be removed directly, for example by some pharmacological adjuvant. Latencies and amplitudes of the various waves are accepted simple features with which to characterize the form of the AER, but there are alternatives[15] to our chosen method of measuring the amplitudes by reference to the preceding peak.

The concentration-related changes in the form of the AER, after 30 min of anaesthesia or sedation with propofol alone, were qualitatively similar to those found by others. However, complete suppression of the AER waveform required greater propofol concentrations than have been described previously.[8 9] This may be attributable to polypharmacy, different filtering of the EEG or pharmacodynamic instability in their studies. Although the brainstem wave V changed much less with propofol

Table 4 Correctness, sensitivity and specificity of the seven best discriminators for the eyelash and venepuncture responses. Dose=final infusion rate of propofol, concentration=blood propofol concentration

AEP variable	Correctness (%)	Sensitivity (%)	Specificity (%)	Threshold
Eyelash response				
Nb latency	98	100	96	53 ms
Basic frequency	98	100	96	30–33 Hz
Superimposability index	98	94	100	
Dose	96	100	89	6.3–7.8 mg kg^{-1} h^{-1}
Pa latency	93	93	93	35−36 ms
Concentration	91	100	79	2.9 μg ml^{-1}
Pa amplitude	91	86	93	0.85–0.98 μV
Venepuncture response				
Concentration	87	91	69	4.8 μg ml^{-1}
Dose	86	89	69	11–12 mg kg^{-1} h^{-1}
Na latency	81	93	53	23.5–24 ms
Pa latency	79	82	69	44 ms
BS latency	76	86	54	7.7 ms
Nb latency	76	79	69	66–68 ms
Superimposability index	76	93	30	

concentration than the later waves, we noticed some changes in its latency (table 2), unlike in other reports.[7 8]

In the absence of particular explanations, such as deafness or hysteria, failure to acknowledge or respond to verbal instructions is probably the simplest indicator of the threshold between consciousness and unconsciousness or anaesthesia. Verbal responses were tested in all patients, but concern about the possible distracting effects of the insert headphones led us to place more reliance on the analysis of eyelash reflex, which has very similar pharmacological and EEG correlates.[10]

With a sensitivity of 100% and specificity of 96%, a threshold Nb latency of 53 ms discriminated between the presence and absence of an eyelash reflex better than any other simple feature and as well as any of the composite features. The scope for improvement seems small, although this may apply only to this particular set of data. For an EEG feature to be useful in clinical monitoring or feedback control, sensitivity in detecting awareness is probably more important than selectivity. False positives (arising from unselectivity) would result in an overdose of anaesthetic agent. This happens in daily anaesthetic practice without being particularly troublesome. In contrast, false negatives (arising from insensitivity to awareness) would leave some patients aware during surgery, a much more serious error. Other workers have also suggested that Nb latency is a useful discriminator[16] but with a threshold value of 44 ms, which would have had a sensitivity of only 43% (although a specificity of 100%) in detecting eyelash responders in our patients. In our work on the unstimulated EEG,[10] a median power frequency of 8.3 Hz had a sensitivity of 94% and specificity of 84%.

One might reasonably expect composite measures to provide better information on the overall form of the AER. The reciprocal of the difference between Na and Nb latencies is the basic low frequency component of the AER. It is related closely to the latency of Nb itself (which accounts for its high discriminating power (table 4)). The awake value of approximately 40 Hz is also the steady state frequency of the awake AER.[17] If auditory stimuli are repeated at a fixed frequency of 40 Hz as sedative or anaesthetic drugs are given, the amplitude of the steady state AER is reduced,[18] presumably because the basic frequency no longer resonates with the stimulating frequency. If the stimulation frequency is changed to match the change in the basic frequency, the amplitude of the steady state AER can be better maintained and the frequency required to do so, "the coherent frequency", is yet another possible correlate of anaesthesia.[19] The first[20] and second[15] differential of the waveform have also been used empirically to describe the transient AER. None of our composite measures seemed to offer any advantage over the simpler Nb latency, although composite measures could be more robust in an automatic analysis environment, such as closed loop control. If any particular single or composite feature in the AER or EEG is to be proposed as a universal predictor of the risk of awareness, it is important that its value be constant in the face of variations. These include the pharmacopoedia to produce anaesthesia and the levels of arousal brought about by surgery or other noxious stimuli. This was not tested in our study.

Our study took approximately 90 s to collect the data for analysis. Although acceptable with stable blood concentrations, it is too long for periods when blood concentrations are changing rapidly. A faster method of obtaining estimates of the AER is needed.

AER features ranked more highly than dose and concentration of propofol as discriminators for the eyelash response. However, the opposite was true for the response to venepuncture (table 4). The observation that the brainstem wave V latency has some discriminatory value for the response to venepuncture accords with the evidence that responses to superficial pain (such as venepuncture) are mediated well below the cortical level.[21] With faster sampling of the EEG signal to resolve the first 10 ms more accurately, the discriminating potential of brainstem responses for pain could possibly be improved.

Better characterization of the AER correlates of different clinically observable responses may improve our understanding of the hierarchy of responsiveness that is challenged by anaesthesia.

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References

1. Heneghan CPH, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. *British Journal of Anaesthesia* 1987; **59**: 277–282.
2. Picton TW, Hillyard SA. Human auditory evoked potentials. II: Effects of attention. *Electroencephalography and Clinical Neurophysiology* 1974; **36**: 191–199.
3. Hillyard SA, Hink RF, Schwent VL, Picton TW. Electrical signs of selective attention in the human brain. *Science* 1973; **182**: 177–180.
4. Schwender D, Kaiser A, Klasing S, Peter K, Poppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 493–501.
5. Andrade J. Learning during anaesthesia: A review. *British Journal of Psychology* 1995; **86**: 479–506.
6. Chassard D, Joubaud A, Colson A, Guiraud M, Dubreuil C, Bansillon V. Auditory evoked potentials during propofol anaesthesia in man. *British Journal of Anaesthesia* 1989; **62**: 522–526.
7. Savoia G, Esposito C, Belfiore F, Amantea B, Cuocolo R. Propofol infusion and auditory evoked potentials. *Anaesthesia* 1988; **42** (Suppl.): 46–49.
8. Thornton C, Konieczko KM, Knight AB, Kaul B, Jones JG, Dore CJ, White DC. Effect of propofol on the auditory evoked response and oesophageal contractility. *British Journal of Anaesthesia* 1989; **63**: 411–417.
9. Schwender D, Golling W, Klasing S, Faber Zullig E, Poppel E, Peter K. Effects of surgical stimulation on midlatency auditory evoked potentials during general anaesthesia with propofol/fentanyl, isoflurane/fentanyl and flunitrazepam/fentanyl. *Anaesthesia* 1994; **49**: 572–578.
10. Forrest FC, Tooley MA, Saunders PR, Prys-Roberts C. Propofol infusion and the suppression of consciousness: the EEG and dose requirements. *British Journal of Anaesthesia* 1994; **72**: 35–41.
11. Regan D. *Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine.* New York: Elsevier Science Publishing Co., Inc, 1989.
12. Roberts FL, Dixon J, Lewis GTR, Tackley RM, Prys-Roberts C. Induction and maintenance of propofol anaesthesia: a manual infusion scheme. *Anaesthesia* 1988; **43**: 14S–17S.
13. Dunnet JM, Prys-Roberts C, Holland DE, Browne BL. Propofol infusion and the suppression of consciousness: dose requirements to induce loss of consciousness and to suppress response to noxious and non-noxious stimuli. *British Journal of Anaesthesia* 1994; **72**: 29–34.
14. Plummer GF. An improved method for the determination of propofol (ICI 35868) in blood. *Journal of Chromatography (Biomedical Applications)* 1987; **421**: 171–176.
15. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; **8**: 89–107.
16. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Dore CJ, Newton DEF, Jones JG. The auditory evoked potential as a indicator of awareness. *British Journal of Anaesthesia* 1989; **63**: 113–115.
17. Galambos R, Makeig S, Talmachoff P. A 40Hz auditory potential recorded from the human scalp. *Proceedings of the National Academy of Sciences USA* 1981; **78**: 2643–2647.
18. Plourde G, Boylan JF. The auditory steady state response during sufentanil anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 683–691.
19. Munglani R, Andrade J, Sapsford DJ, Baddeley A, Jones JG. A measure of consciousness and memory during isoflurane administration: the coherent frequency. *British Journal of Anaesthesia* 1993; **71**: 633–641.
20. Kenny GNC, Mantzaridis H, Fisher AC. Validation of monitoring anaesthetic depth by closed-loop control. In: Sebel PS, Bonke B, Winograd E, eds. *Memory and Awareness in Anaesthesia.* New Jersey: Englewood Cliffs, 1993; 255–264.
21. King BS, Rampil IJ. Anesthetic depression of spinal motor neurons may contribute to lack of movement in response to noxious stimuli. *Anesthesiology* 1994; **81**: 1484–1492.

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Comparison of patient-controlled sedation with either methohexitone or propofol

S. K. HAMID, N. MCCANN, L. MCARDLE AND A. J. ASBURY

Summary

We studied 42 patients undergoing oral surgery under local anaesthesia with i.v. sedation, allocated randomly to receive either methohexitone (group M) or propofol (group P) for patient-controlled sedation (PCS). Group M patients self-administered 2.5-mg (0.5 ml) bolus doses of methohexitone and group P, 5-mg (0.5 ml) doses of propofol, without a lockout. The 0.5-ml bolus dose was delivered over 7.2 s for both drugs. The procedure was completed satisfactorily in all patients. Patients in both groups achieved their desired levels of sedation. No patient lost verbal contact. Group M patients had higher heart rates during the procedure. The lowest Sp_{O_2} values recorded were 92% and 95% for group P and group M, respectively. Immediately after operation patients in group M reported that they felt more sleepy than those in group P ($P < 0.01$) but there were no differences at subsequent times. The results of the psychomotor tests were comparable for the two groups after operation, except for the "posting box task" at 15 min after operation when the mean decrement (compared with preoperative performance) was −3% for group P and −13% for group M ($P < 0.05$). More patients in group P complained of pain in their hand. We conclude that methohexitone is a suitable alternative drug to propofol for PCS. (*Br. J. Anaesth.* 1996; **77**: 727–730)

Key words
Anaesthetics i.v., methohexitone. Anaesthetics i.v., propofol. Sedation, patient-controlled. Surgery, oral.

Patient-controlled sedation (PCS) has been reported using either midazolam or propofol. However, they are not comparable in pharmacokinetics. Oversedation may be a problem with midazolam as it has a relatively slow onset and the patient may make additional demands for drug boluses before adequate time has elapsed for the earlier boluses to produce an effect. The use of methohexitone for PCS has not been described. It is cleared rapidly from the body and is cheaper than propofol.[1] Studies of psychomotor function after induction doses of propofol or methohexitone suggest that there is faster recovery of psychomotor performance after propofol.[2–4] However, MacKenzie and Grant showed that propofol produces a slightly greater decrease in the critical flicker fusion threshold than methohexitone.[5] A comparison of psychomotor performance after sedation with propofol or methohexitone has not been performed.

Methohexitone may be a more suitable alternative than midazolam for day-case PCS. The objective of this prospective, randomized study was to compare PCS with either methohexitone or propofol.

Patients and methods

Approval was obtained from the hospital Ethics Committee and we studied 42 unpremedicated patients, ASA I or II, aged 16 yr or more, undergoing oral surgery under local anaesthesia with i.v. sedation. Patients gave informed consent. Exclusion criteria included patients who were taking sedative medication, those who were pregnant and those who had previous adverse reactions to propofol or methohexitone. After a full explanation, patients were allocated randomly to receive PCS with either methohexitone (group M) or propofol (group P). Randomization was performed using sealed envelopes. Each drug was self-administered by the patient from a Graseby 3300 infusion pump. The bolus dose administered was 0.5 ml for both drugs. The concentrations of drugs used were 10 mg ml^{-1} for propofol and 5 mg ml^{-1} for methohexitone; hence group M patients received 2.5 mg of methohexitone and those in group P received 5 mg of propofol on demand. No lockout time was used but as the infusion rate was 250 ml h^{-1}, it took 7.2 s to infuse the 0.5-ml bolus. Demands made for drug during this period resulted in no drug being administered.

Patients were instructed in the use of the infusion pump before sedation and were told that they could press the demand button as often as they liked to produce the level of sedation they desired but that the pump would not administer another dose for a

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period of approximately 7 s. A maximum of 8 doses per minute could be administered, giving a maximum of 20 mg of methohexitone or 40 mg of propofol per minute. Before sedation and surgery, immediately after operation and at 15 and 30 min after the end of the procedure, patients were asked to rate their anxiety, pain and somnolence on a four-point scale (none, mild, moderate and severe). They were also asked to complete a Corah dental anxiety questionnaire before operation.[6]

Patients performed psychomotor tests before operation and again immediately on completion of the procedure and at 15 and 30 min. These tests consisted of a "posting box task" (PBX) which involved the patient putting 15 shaped bricks through appropriately shaped holes of a box as quickly as possible using one hand.[7] The best time for two attempts for the PBX task was taken. The other test consisted of a choice reaction time (CRT) which was measured using a programme implemented on a hand-held Psion organizer.[8] Before the CRT test itself, preliminary instructions scroll across the screen, prompted by key presses by the patient. The final message is "Are you ready?—press the Y key to go on". After the patient presses the Y key, one of six letters (A–F) appears on the screen in random order and after a randomized time interval. The patient has to press the corresponding letter on the keyboard. This process is repeated 30 times. This test gave two results: a choice reaction time score (CRTS), that is the percentage of choices made correctly, and a mean choice reaction time (CRTM), that is the mean time taken to react. At the end of the test, the Psion displays the results which are stored and can be transferred subsequently to an IBM-compatible computer for manipulation by word-processing and spreadsheet programmes.

When the patient was settled in the dental chair, monitoring (non-invasive arterial pressure, heart rate and pulse oximetry) was established and continued throughout the procedure. A 20-gauge cannula was inserted into a vein on the dorsum of the patient's hand. For event timing, time 0 was taken as the time of administration of the first dose of drug. The patient's deepest level of sedation was recorded using a modified published five-point scale.[9] This was recorded every 1 min for the first 16 min, every 2 min for the next 15 min and every 5 min until the end of the dental procedure (table 1). Local anaesthetic infiltration (2% lignocaine with adrenaline 1:80 000) was performed by the dentist when the patient was ready.

After completion of the dental procedure, the patient was transferred to a recovery area. Before discharge home, patients were questioned on nausea, pain in the hand, recall of intraoperative events, if they had managed to achieve their desired level of sedation and if they would be prepared to have the same method of sedation again. Patients and the dentist were asked to evaluate the acceptability of the sedation technique using a four-point scale (poor, moderate, good or excellent). The dentist was also asked to evaluate patient cooperation during the procedure.

Table 1 Sedation scoring used

1=Fully awake
2=Drowsy with eyes open and/or brisk response to command
3=Drowsy with eyes closed and/or slow response to command
4=Eyes closed but rousable with mild physical stimulus
5=Eyes closed and unrousable with mild physical stimulus

Minitab for DOS release 7 was used for statistical analysis. The Mann–Whitney test was used for ordinal data, and chi-square test for nominal data. A probability (P) of less than 0.05 was considered to be statistically significant.

Results

Forty patients were included in the data analysis; two patients were excluded, one in group M had a cannula resited during the procedure and the other patient in group P had to be given a general anaesthetic to reduce a dislocated jaw. There were 20 patients in each group. Fourteen patients in group M had third molar teeth extractions, two had extraction of other teeth, two had apicectomies, one had excision of a granuloma of the mouth and one had removal of a salivary calculus. Six patients in group P had third molar teeth extractions, eight had extraction of other teeth and six had apicectomies. The proposed dental procedure was completed satisfactorily in all patients (table 2).

The lowest oxygen saturation value recorded was 92% for a group P patient and 95% for a group M patient. Group M patients had higher heart rates during the procedure. Mean arterial pressures remained within acceptable clinical limits and were similar in the two groups. The ratio of successful to unsuccessful demands was similar in both groups.

No patient in either group lost verbal contact. Table 3 shows the deepest level of sedation achieved by the patients. All patients were discharged approximately 30 min after the end of the procedure. Immediately on arrival in the recovery area patients in group M reported that they felt drowsier than those in group P ($P < 0.01$). However, there were no

Table 2 Summary data for patients and procedures (median (IQR))

Group	Methohexitone	Propofol
Age (yr)	26 (12)	36 (20)
Sex (M:F)	5:15	4:16
Weight (kg)	62 (23)	66 (20)
Total dose (mg)	130 (127)	223 (126)
Successful:unsuccessful PCS demands	0.89 (0.4)	0.92 (0.2)
Start local anaesthetic (min)	7.0 (4)	7.5 (4)
Procedure duration (min)	18 (29)	21 (25)

Table 3 Deepest level of sedation achieved by the patients in the intraoperative period

	Sedation score				
	1	2	3	4	5
Group M (n)	0	16	4	0	0
Group P (n)	0	14	6	0	0

Table 4 Patient scoring of their drowsiness. Patient sedation score 1= not at all sleepy, 2= mildly sleepy, 3= moderately sleepy, 4= extremely sleepy. The sedation scores immediately after operation for the methohexitone group were significantly different ($P < 0.01$) from the propofol group

	Sedation score			
	1	2	3	4
Immediately after operation				
Group M (*n*)	0	11	5	4
Group P (*n*)	5	13	2	0
15 min after operation				
Group M (*n*)	8	10	1	1
Group P (*n*)	11	8	1	0
30 min after operation				
Group M (*n*)	14	6	0	0
Group P (*n*)	7	3	0	0

Table 5 Median (IQR2) percentage changes in individual performance of the psychomotor tests compared with preoperative values $^*P < 0.05$

	Time (min)		
	0	15	30
PBX			
Group M	−20 (28)	−7 (14) *	4.5 (15)
Group P	−18 (24)	0 (15)	0 (15)
CRTS			
Group M	0 (3)	0 (0)	0 (0)
Group P	0 (1)	0 (0)	0 (3)
CRTM			
Group M	26 (26)	2 (8)	4 (11)
Group P	28 (14)	3 (9)	8 (12)

significant differences at 15 or 30 min after operation. Table 4 shows how sedated patients said they felt immediately after, 15 min and 30 min after the procedure.

Table 5 shows the results of psychomotor testing. Group M patients showed a greater decrement in the PBX task at 15 min than those in group P. However, there were no significant differences in performance times immediately after or 30 min after the procedure. CRTS and CRTM were not significantly different between the two groups at any time after operation.

Two patients in group M had some fine tremor-like movements of their limbs of short duration but this did not upset the patient or dentist. Four patients in group M and nine patients in group P complained of pain in their hand but this was not statistically significant. Eleven patients in group M and 12 in group P had amnesia for certain intraoperative events. One patient in each group had amnesia for recovery room events. No patient complained of nausea or vomited. All patients said that they had managed to achieve their desired level of sedation. All patients thought their sedation was either good or excellent. Patient cooperation was rated as excellent in 19 patients and poor in one patient in group M and excellent in 15 and poor in one patient in group P.

Discussion

Our study has shown that methohexitone compared favourably with propofol when used for patient-controlled sedation. However, patients who received methohexitone reported that they felt more drowsy immediately after the procedure than those who received propofol. Fifteen minutes after surgery both groups felt less drowsy and there was no difference between the groups at this time or subsequently. More patients in the methohexitone group had wisdom teeth extractions. This could have resulted in an increased demand for sedation by this group.

The methohexitone group performed the PBX more slowly than the propofol group 15 min after the procedure. Immediately and 30 min after the procedure there were no significant differences in performance times. However, this is a fairly insensitive test.[10] There were no differences between the two groups in CRTM and CRTS at any time after operation.

All patients were discharged home escorted 30 min after operation with written instructions. Studies comparing PCS with propofol or midazolam suggest faster recovery of psychomotor function in patients who received propofol.[11 12] The amnesic effects of propofol and methohexitone appeared to be similar when used for sedation in this study, with the most marked effect being amnesia for intraoperative events. Amnesia is more likely to persist for recovery events with midazolam.[12] Hence methohexitone and propofol would be more suitable agents for day-case patients requiring sedation.

More patients in the propofol group complained of pain in the hand but this was not statistically significant. The lower incidence of pain in the hand than would have been expected for the methohexitone patients may have been because of the more dilute concentration (0.5%) of methohexitone used in this study.

Patients were allowed to start and maintain their own sedation. The amount of drug administered was limited by the drug concentration and the time taken to infuse each dose. The infusion rate of the pump used in this study was 250 ml h^{-1}. If a pump capable of infusing at a faster rate had been used, then a faster onset time for sedation would have been achieved. However, this may have risked the patient being oversedated. No patient lost verbal contact and all patients were satisfied with their level of sedation. An initial bolus dose of drug was not administered because of individual patient requirements for depth of sedation.

The anaesthetist who carried out the intraoperative sedation assessment and the dentist were not blinded and this may have resulted in some bias of the intraoperative results but the anaesthetist who carried out the postoperative assessments was blinded to the agent used.

It must be stressed that although we were able to maintain verbal contact with all patients throughout the procedure, it is imperative that personnel skilled in airway management and resuscitation are present during sedation procedures. Equipment and drugs used for resuscitation must be at hand.

References

1. Briemer DD. Pharmacokinetics of methohexitone following intravenous infusion in humans. *British Journal of Anaesthesia* 1976; **48**: 643–648.
2. MacKenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *British Journal of Anaesthesia* 1985; 57: 725–731.
3. Raeder JC, Misvaer G. Comparison of propofol induction with thiopentone or methohexitone in short outpatient general anaesthesia. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 607–613.
4. Kay B, Healey TEJ. Propofol ('Diprivan') for outpatient cystoscopy: efficacy and recovery compared with althesin and methohexitone. *Postgraduate Medical Journal* 1985; **61**: 108–114.
5. MacKenzie N, Grant I. Comparison of propofol with methohexitone in the provision of anaesthesia for surgery under regional blockade. *British Journal of Anaesthesia* 1985; **57**: 1167–1172.
6. Corah NL Development of a dental anxiety scale. *Journal of Dental Research* 1969; **48**: 596.
7. Craig J, Cooper GM, Sear JW. Recovery from day-case anaesthesia—comparison between methohexitone, althesin and etomidate. *British Journal of Anaesthesia* 1982; **54**: 447–451.
8. Hickey S, Asbury AJ, Millar K. Psychomotor recovery after outpatient anaesthesia: Individual impairment may be masked by group analysis. *British Journal of Anaesthesia* 1991; **66**: 345–352.
9. Wilson E, David A, MacKenzie N, Grant IS. Sedation during spinal anaesthesia: comparison of propofol and midazolam. *British Journal of Anaesthesia* 1990; **64**: 48–52.
10. Hindmarch I, Bhatti JZ. Recovery of cognitive and psychomotor function following anaesthesia. A review. In: Hindmarch I, Jones JG, Moss E, eds. *Aspects of Recovery from Anaesthesia*. Chichester: Wiley, 1987; 113–165.
11. Cook LB, Lockwood GG, Moore CM, Whitwam JG. True patient-controlled sedation. *Anaesthesia* 1993; **48**: 1039–1044.
12. Rudkin GE, Osborne GA, Finn BP, Jarvis DA, Vickers D. Intra-operative patient-controlled sedation. Comparison of patient-controlled propofol with patient-controlled midazolam. *Anaesthesia* 1992; **47**: 376–381.

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Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation†

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Summary

Patients in the intensive care unit require large doses of sedative/analgesic drugs to tolerate the presence of a tracheal tube and other unpleasant stimuli. The ideal regimen for sedatives and analgesics has not yet been found. We have investigated the effects of topical local anaesthesia to the pharynx and airway on sedative/analgesic requirements in 30 ICU patients (25–75 yr old) with no obvious brain injury, undergoing mechanical ventilation. Oral tracheal tubes were changed to a modified tube which allowed instillation of local anaesthetic solutions onto the pharyngeal, laryngeal and tracheal mucosa. Lignocaine 1% (5 ml) or 5 ml of 0.9% saline were instilled hourly for 12 h each for a total of 24 h, in a double-blind, randomized crossover design. Baseline sedation was maintained with propofol or alfentanil infusions, or both, which were titrated to patient comfort and to maintain an optimum sedation score throughout. Twenty-five patients completed the study. Mean total propofol and alfentanil requirements were 766 (SD 524) mg and 17 (7.6) mg, respectively, during 12 h of lignocaine instillation, and 1321 (862) mg and 25 (11.4) mg, respectively, during 12 h of saline instillation. There was a significant reduction ($P<0.05$) in the requirements for both agents during the period of lignocaine instillation. (*Br. J. Anaesth.* 1996; **77**: 731–734)

Key words

Anaesthetics local, lignocaine. Intensive care, sedation. Anaesthetics i.v., propofol. Anaesthetics i.v., alfentanil. Ventilation, artificial. Airway, mucosa.

Translaryngeal tracheal intubation is the standard technique for early airway management of patients requiring assisted ventilation. Most patients require anaesthesia or significant amounts of sedatives/analgesics to tolerate a tracheal tube for the first few days in the ICU.[1 2] This requirement is unimportant during surgery but is often a major drawback in patients requiring intensive care as these drugs often accumulate in the critically ill patient, and may increase the length of stay, morbidity and mortality.[3]

Tracheal intubation can be performed in awake patients using topical local anaesthesia to the airway in difficult intubation situations.[4] We were interested to determine if topical lignocaine delivered via a modified tracheal tube (LITA tube—laryngotracheal instillation of topical anaesthesia) to the pharyngeal, laryngeal and tracheal mucosa could improve comfort, and thereby reduce requirements of sedative and analgesic drugs in ICU patients. Topical lignocaine via an LITA tube has been reported to reduce the incidence of tracheal tube-induced coughing during emergence from general anaesthesia.[5] The use of this tube has not been described previously in patients requiring intensive care.

Patients and methods

After obtaining approval from the local Ethics Committee and written informed consent from the patients' relatives, we enrolled 30 patients (23 males) requiring ventilatory support in the ICU. We excluded patients requiring analgesia in the immediate postoperative period and those with obvious brain injury. Oral tracheal tubes were changed to an LITA tube of 8 mm id in females and 8.5 mm id in males (fig. 1) after administration of an i.v. bolus of propofol 0.5–1.5 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. The study began 2 h later.

The LITA tube (Sheridan Catheter Corp., Argyle, NY, USA) differs from a conventional tracheal tube only in that it contains an additional small-bore channel incorporated into the wall of the lesser curvature of the tube (fig. 1). The proximal end of this channel has a Luer-lock syringe connector and has 10 small perforations on its distal segment. Local anaesthetic, injected under pressure, sprays the mucosa both proximal and distal to the inflated tube cuff. It is designed so that the spray of local anaesthetic deflects off the anterior wall of the larynx and trachea and by gravity runs down to bathe the entire circumference of the mucosa.

Syringes containing 5 ml of either 1% lignocaine or 0.9% saline were prepared by the hospital pharmacy. The authors and the nursing staff were blinded to the nature of the solutions.

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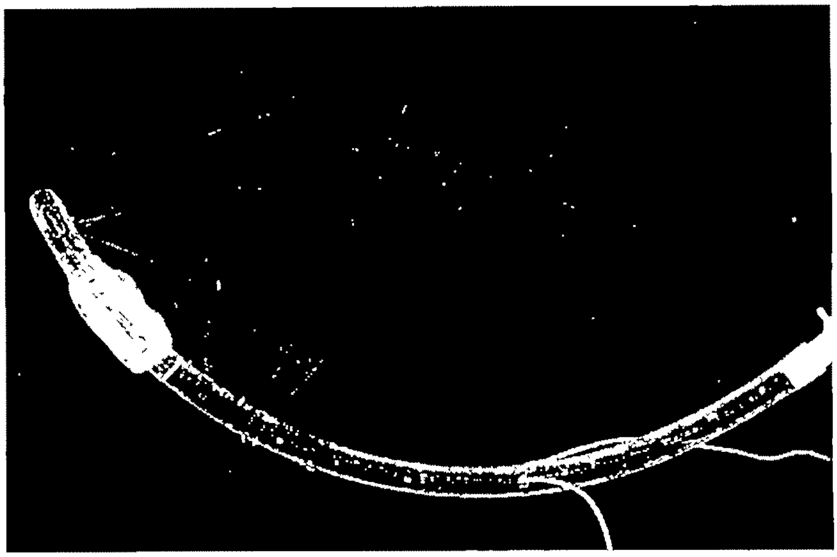

Figure 1 Local anaesthetic injected via the delivery channel of the the LITA tracheal tube exits through the holes in a fine spray both proximal and distal to the cuff.

Table 1 Sedation score

Level 1	= Patient restless, agitated or anxious, compromising ventilation and oxygenation, showing signs of distress on physiotherapy, tracheal suction, oropharyngeal suction and handling in general.
Level 2	= Patient awake but needs sedation for physiotherapy and other nursing or invasive procedures.
Level 3	= Patient just asleep, responds to speech and touch, needs additional sedation to cover handling and physiotherapy or any other procedures.
Level 4	= Patient asleep, handles well and tolerates care, showing response to speech and to touch by either squeezing the nurses hand or by blinking.
Level 5	= Patient asleep, has dull/sluggish response to any form of stimulation, for example tracheal suction
Level 6	= Patient asleep showing no sign of response to stimulation of any kind.

Randomization was carried out by the pharmacy according to a computer-generated table so that each patient received an hourly instillation via the LITA tube of either 1% lignocaine for the initial 12 h and saline for the ensuing 12 h or vice versa. Each patient acted as their own control. We chose the 1% lignocaine solution as we know that this acts on bronchial mucosa during fibreoptic bronchoscopy and we wished to avoid potential local anaesthetic toxicity from absorption of more concentrated solutions.

Sedation was maintained with baseline infusions of propofol 0.2–1 mg $kg^{-1} h^{-1}$ or alfentanil 10–20 μg $kg^{-1} h^{-1}$, or both. We chose these particular agents for their short duration of action and ability to rapidly titrate doses for a desired effect. The level of sedation was monitored hourly using a sedation scale (table 1) with six levels of cognitive neurological function, similar to the Ramsay sedation scale.[6] Monitoring of sedation and adjustment of propofol and alfentanil infusions to maintain a target score of 3–4 (table 1) were carried out throughout the entire study. If at any time sedation was assessed to be outside the target level, nurses achieved the target sedation levels either by administering additional boluses of either propofol 10 mg or alfentanil 200 μg or by altering the infusion rates. Episodes of coughing and gagging, desaturation (Sa_{O_2}<90%) and hypertension (increase in systolic arterial pressure >20% above baseline) were recorded during the study. Patients who were awake enough were questioned about the discomfort caused by the presence of the tracheal tube or by pulmonary suctioning. The paired *t* test in SPSS version for MS Window release 6.1 was used to assess statistical significance between sedation requirements during the different periods, and significance was taken at $P<0.05$.

Results

We studied 30 patients, aged 25–75 yr; the male:female ratio was 3.3:1. Patients were of a mixed group (table 2) and they had no significant organ dysfunction except respiratory failure. No problems were encountered during change of the tracheal tube to an LITA tube. Five patients were excluded from subsequent analysis because the study was not completed: in two of these the trachea was extubated, one after 3 h and a second after 8 h from the start of the study, one required neuromuscular block 5 h after the beginning of the study because of deterioration in oxygenation, one was transferred to another hospital and another developed bronchospasm during the period of saline instillation. Thirteen of the remaining patients received lignocaine instillations for the initial 12 h followed by 12 h of saline instillation. The remainder started with saline instillation. Eight patients received a propofol infusion, eight patients an alfentanil infusion and another nine patients received both concurrently during the study. The total amount of propofol and alfentanil used for each patient was recorded for the 12-h pre-study period, for lignocaine instillation and for the 12 h of saline instillation. Mean requirements of propofol and alfentanil are shown in table 3. There was a significant reduction (30–40%) in the requirements of both drugs during lignocaine instillation compared with the pre-study and saline periods. There was no significant difference between the requirements for

Table 2 Patient data including primary diagnosis, day of stay when the study was undertaken, duration of ventilatory support and ICU stay, and overall survival of 25 patients. *Includes all patients. †Respiratory failure developed after postoperative day 4. ITP=Idiopathic thrombocytopenic purpura

n	Age (yr)	Sex (M/F)	Diagnosis	Day of study	Duration of ventilation (days)	ICU stay (days)	Survival
13	62.5 (55–75)	9/4	COAD, respiratory failure	2nd	4.5 (1.5)*	5.3 (2.5)*	88%*
9	53 (45–65)	7/2	Postop. resp. failure†	2nd			
2	55, 62	2/0	Pulmonary oedema	2nd			
1	25	0/1	ITP, respiratory failure	3rd			

Table 3 Propofol and alfentanil requirements (mean (SD)) during periods of saline and lignocaine instillations in 25 patients and in a subgroup of 13 patients with COAD. $*P<0.05$, $**P<0.01$; $***P<0.001$

Total (mg)	Pre-study (12h)	Lignocaine (12 h)	Saline (12h)
All patients (*n*=25)			
Propofol (*n*=17)	1573 (632)	766 (524)**	1321 (862)
Alfentanil (*n*=17)	30.8 (8.75)	17.5 (7.6)***	25 (11.4)
Patients with COAD (*n*=13)			
Propofol (*n*=7)	1776 (795)	816 (604)***	1532 (944)
Alfentanil (*n*=9)	34.5 (7.95)	17 (9.3)*	28 (11.6)

propofol or alfentanil in the pre-study and saline periods. We analysed a subgroup (table 3) of 13 COAD patients. Three received both a propofol and an alfentanil infusion, four a propofol infusion and another six patients received an alfentanil infusion during the study. This group was found to have a more marked reduction in requirements for propofol and alfentanil (40–50%).

Mean sedation scores during the 12 h before entering the study were 4–6 while a score of 3–4 was maintained during the study. Nine patients were awake and co-operative (sedation score of 2) during the study. They appeared to be less bothered by pulmonary suctioning during the period of lignocaine instillation compared with saline instillation. We noted that patients also tended to cough and were transiently restless in response to tracheal instillation of saline. No episode of desaturation ($Sa_{O_2}<90\%$) or hypertensive response (increase in systolic arterial pressure by more than 20% from baseline) was reported during periods of lignocaine or saline instillation.

Discussion

Patients undergoing mechanical ventilation are subjected to many noxious stimuli attributable to diagnostic, therapeutic and physical nursing interventions. The presence of a tracheal tube and frequent tracheal suctioning are very unpleasant. An optimal level of sedation is a fundamental requirement to facilitate delivery of ICU care. Although essential, sedation and analgesia in this group of patients produce many side effects; cardiovascular instability, delayed weaning from mechanical ventilation, impaired tolerance of enteral feeding, tolerance and withdrawal symptoms, and other complications of immobility.[3] These effects may persist because of accumulation of the parent drugs and their metabolites in critically ill patients.

Various strategies have been adopted to reduce sedative and analgesic requirements, and hence their side effects, without compromising patient comfort. These include tracheotomy, non-invasive ventilation, regional nerve block to wounds whenever appropriate, and synchronization of mechanical ventilation. Tracheotomy is generally claimed to be tolerated better in patients undergoing ventilation.[7 8] Non-invasive ventilation in patients with respiratory failure has a better outcome compared with intubation and conventional IPPV.[9] However, at the present time, most patients in the ICU require a tracheal tube in order to achieve adequate ventilation and provide access to the lower airway for removal of secretions.

In this study, we have demonstrated that propofol and alfentanil requirements were significantly lower (overall reduction 30–40%) during the period of hourly laryngotracheal instillation of lignocaine via an LITA tube than during the period of saline instillation. The results in a subgroup of 13 COAD patients showed more marked reduction in the total amount of sedatives during 12 h of lignocaine instillation. We believe this could be ascribed to the absence of any major stimuli (e.g. wounds) in these patients other than the tracheal tube and frequent tracheal suction.

During awake tracheal intubation and bronchoscopy, a higher concentration (4% or 10%) of local anaesthetic is used for airway anaesthesia. Lignocaine 1% instilled via an LITA tube has been shown to decrease the incidence of coughing and bucking during emergence from general anaesthesia.[5] A survey of the literature gives very little information on topical airway anaesthesia, including optimal choice of drug, dose and frequency of administration. This study was the first of its type and so we had to choose the doses empirically. We used 1% lignocaine to reduce potential lignocaine toxicity and to instill a larger volume (5 ml hourly) to allow spread throughout the tracheal and laryngeal mucosa. This would not have been possible with a smaller volume of 4% lignocaine.

We chose propofol or alfentanil, or both, as the sedative/analgesic agents in this study to allow rapid titration of the level of sedation when used as an i.v. infusion, either alone or in combination.[10] Propofol potentiates the analgesic effects of alfentanil and the latter potentiates the sedative action of propofol.[11] Infusion of alfentanil was used alone in eight patients who were haemodynamically unstable and propofol infusion was used alone in another eight patients in whom nasogastric aspirate was high and who showed intolerance to nasogastric feeding.

The patients' levels of sedation and anxiety were assessed using a six-point scale similar to the Ramsay sedation scale. Monitoring the degree of sedation in the ICU is inexact. However, the Ramsay scale is the most widely used scoring system in clinical studies in critically ill patients. This scale evaluates the patient either in the awake or asleep state but does not convey information on the quality of sedation. Other authors have commented on the need for a new validated tool and scale to measure the efficacy of sedation in the ICU.[12]

Saline may not be a true control as patients cough and become restless for a few minutes in response to its instillation. However, it did not increase the requirement of sedatives during the period of saline instillation compared with the pre-study period. Bronchospasm developed in one patient who had an acute exacerbation of COAD during the period of saline instillation and this may have been precipitated by the saline. Hence, we felt that it was reasonable to use saline as a control as otherwise it would have been difficult to carry out the study in a blinded fashion.

The total dose of lignocaine was 600 mg over 12 h. The dose of lignocaine used for treatment of ventricular arrhythmias is significantly greater[13] and we believe it is unlikely that toxicity would occur given the dose and duration of this study. Lignocaine is known to be absorbed rapidly from the tracheobronchial mucosa. We cannot exclude the effect of systemically absorbed lignocaine from our findings. However, studies investigating the effects of i.v. lignocaine as an antitussive and an agent to attenuate the cardiovascular response to intubation are inconclusive.[14 15] The short period of this study did not allow us to assess if tolerance to the local anaesthetic occurred. Local anaesthetics with a longer duration of action (e.g. bupivacaine) may be beneficial but there is a paucity of data on the mucosal use of such drugs.

References

1. Bion J. Sedation and analgesia in the intensive care unit. *Hospital Update* 1988; **14**: 272.
2. Paiement B, Boulanger M, Jones CW, Roy M. Intubation and other experiences in cardiac surgery: The consumer's views. *Canadian Anaesthetists Society Journal* 1979; **26**: 173.
3. Prielipp RC, Coursin DB, Wood KE, Murray MJ. Complications associated with sedatives and neuromuscular blocking drugs in critically ill patients. *Critical Care Clinics* 1995; **11**: 983–1003.
4. Reasoner DK, Warner DS, Todd MM, Hunt SW, Kirchner J. A comparison of anesthetic techniques for awake intubation in neurosurgical patients. *Journal of Neurosurgical Anesthesiology* 1995; **7**: 94–99.
5. Gonzalez RM, Bjerke RJ, Drobycki T, Stapelfeldt WH, Green JM, Janowitz MJ, Clark M. Prevention of endotracheal tube-induced coughing during emergence from general anesthesia. *Anesthesia and Analgesia* 1994; **79**: 792–795.
6. Ramsay MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone–alphadolone. *British Medical Journal* 1974; **2**: 656–659.
7. Rodriguez JL, Steinberg SM, Luchetti FA, Gibbons KJ, Taheri PA, Flint LM. Early tracheostomy for primary airway management in the surgical critical care setting. *Surgery* 1990; **108**: 655–659.
8. Nicolaou AJ, Tofte B, Leech RC, Beaumont AC. Early tracheostomy in ICU for patients with acute exacerbation of chronic obstructive pulmonary disease. *British Journal of Anaesthesia* 1995; **74**: A363.
9. Broachard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, Isabey D, Harf A. Noninvasive ventilation for acute exacerbation of COAD. *New England Journal of Medicine* 1995; **333**: 817–822.
10. Harper S, Buckley P, Carr K. Propofol and alfentanil for sedation in intensive therapy. *European Journal of Anaesthesiology* 1991; **8**: 157.
11. Pavlin DJ, Coda B, Shen DD, Tschanz J, Nguyen Q, Schaffer R, Donaldson G, Jacobson RC, Chapman CR. Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. *Anesthesiology* 1996; **84**: 23–37.
12. Hansen-Flaschen J, Cowen J, Polomano RC. Beyond the Ramsay scale: need for a validated measure of sedating drug efficacy in the intensive care unit. *Critical Care Medicine* 1994; **22**: 732–733.
13. Hilleman DE, Mohiuddin SM, Mooss AN, Hunter CB, Destache CJ, Sketch MH Sr. Comparative pharmacodynamics of intravenous lidocaine in patients with acute and chronic ventricular arrhythmias. *Annals of Pharmacotherapy* 1992; **26**: 763–767.
14. Yukioka H, Hayashi M, Terai T, Fujimore M. Intravenous lidocaine as suppressant of coughing during tracheal intubation in elderly patients. *Anesthesia and Analgesia* 1993; **77**: 309–312.
15. Singh H, Vichitvejpaisal P, Gaines GY, White PF. Comparative effects of lidocaine, esmolol, and nitroglycerin in modifying the hemodynamic response to laryngoscopy and intubation. *Journal of Clinical Anaesthesia* 1995; **7**: 5–8.

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Comparative effects of thiopentone and propofol on respiratory resistance after tracheal intubation

R. S. C. Wu, K. C. Wu, D. C. W. Sum and M. J. Bishop

Summary

To compare the effects of propofol and thiopentone on tracheal intubation-induced bronchoconstriction, 37 patients were allocated randomly to anaesthesia with either thiopentone 4 mg kg^{-1} followed by a 15-mg kg^{-1} h^{-1} continuous infusion or propofol 3 mg kg^{-1} followed by a 9-mg kg^{-1} h^{-1} continuous infusion. Intubation was facilitated by vecuronium 0.1–0.2 mg kg^{-1}. Respiratory system resistance (*R*rs) was measured by a CP-100 pulmonary function monitor, 5 min after intubation. The 5-min post-intubation *R*rs values were significantly lower in the propofol group (8.5 (SD 1.5) cm H_2O litre^{-1} s^{-1}) than in the thiopentone group (10.9 (3.2) cm H_2O litre^{-1} s^{-1}). Thirty minutes after commencing isoflurane–nitrous oxide anaesthesia, *R*rs declined by 17.5 (SEM 3.6) % from baseline in the thiopentone group, but by only 1.6 (2.6) % in the propofol group. We conclude that the dose of propofol administered provided more protection against tracheal intubation-induced bronchoconstriction than an induction dose of thiopentone. (*Br. J. Anaesth.* 1996; **77**: 735–738)

Key words
Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Intubation tracheal. Complications, bronchospasm.

Bronchoconstriction may occur after tracheal intubation[1–3] and occasionally may be severe enough to produce life-threatening decreases in gas flow. Because induction is the period of highest risk for bronchospasm it is important to identify induction agents which minimize the bronchoconstrictor response to tracheal intubation.

The effects of thiopentone on airway resistance remain controversial. Early studies indicated that thiopentone releases histamine and constricts airways.[4–6] However, thiopentone may also inhibit vagal reflexes,[7] and at higher concentrations produce bronchodilatation.[8] The effects of propofol on human bronchomotor tone are also inconclusive. There are studies reporting bronchospasm during propofol induction[9] but there are also some stating otherwise.[10] Mehr and Linderman, comparing the effects of propofol on peripheral airway responsiveness with the effects of thiopentone and halothane, showed that propofol afforded no benefit over thiopentone or halothane.[11] Cheng and colleagues recently found that *in vitro*, propofol did not produce smooth muscle relaxation.[12] However, a study comparing the incidence of wheezing in asthmatic patients induced by different i.v. anaesthetic agents found that fewer patients wheezed after receiving propofol compared with a barbiturate.[13]

The purposes of this study were to compare the effects of propofol and thiopentone on tracheal intubation-induced bronchoconstriction and to investigate how the addition of an inhalation anaesthetic further influences bronchomotor tone after intubation.

Patients and methods

This study was carried out with the approval of the Human Subjects Review Board of Chang Gung Memorial Hospital. All patients underwent surgery of the extremities and were of normal body habitus, ASA I or II.

After obtaining informed consent, 37 patients, aged 20–50 yr, were allocated to one of two groups. Induction was performed by an anaesthetist who did not participate in the study. The induction agent chosen was according to a random number design which was not revealed until the start of induction. The anaesthetist recording the resistance measurement was unaware of the medication used for induction. Anaesthesia in the thiopentone group was induced with thiopentone 5 mg kg^{-1} i.v. There was a variance allowed of 1 mg kg^{-1} depending on the response of the patient. Vecuronium 0.1–0.2 mg kg^{-1} was given to facilitate oral tracheal intubation using a 7.5-mm tube. After intubation, an i.v. infusion of thiopentone 15 mg kg^{-1} h^{-1} was started immediately to maintain an adequate anaesthetic level until the end of the study. Anaesthesia in the propofol group was induced with 2.5 mg kg^{-1} and a bolus dose of vecuronium followed by a continuous infusion of propofol 9 mg kg^{-1} h^{-1} for maintenance

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of anaesthesia. Patients' lungs were ventilated with 100% oxygen using a Drager Narkomed II ventilator (North American Drager, PA, USA) at a tidal volume of 650 ml, an inspiratory flow rate of 0.6 litre s^{-1} with a rectangular wave pattern and a ventilatory frequency of 10 bpm. Mean end-tidal $P\mathrm{CO_2}$ was 4.6 kPa in the thiopentone and propofol groups. All patients were positioned supine.

Resistance of the respiratory system (*R*rs) was measured 2 and 5 min after intubation with a CP-100 pulmonary function monitor (Bicore, Irvine, CA, USA). The CP-100 pulmonary function monitor is a monitoring device consisting of a flow transducer (VarFlex) and an oesophageal balloon catheter which allows breath-by-breath measurement of tidal volume ($V\mathrm{T}$), airway flow ($\dot{V}$), transpulmonary pressure (airway − oesophageal pressure) and airway pressure (*P*aw). The flow transducer was connected to the ventilation system between the tracheal tube and the Y-piece. The oesophageal balloon catheter was left exposed to ambient pressure to measure *R*rs. Measurement of *R*rs was based on pressure and flow measurements in the airway. Resistance measurements were calculated using the isovolume method (the difference in airway pressure divided by the sum of the flows taken at the same volume during both inspiration and expiration)[14–17] and included resistance of the tracheal tube. The CP-100 monitor is equipped with self-diagnostic hardware tests which perform self-calibration of the measuring system.

After the 5-min period during which the patient received only the induction agent, inhalation anaesthesia was begun with 1.3% isoflurane and 50% nitrous oxide in oxygen, as monitored by end-tidal concentrations. Inspired concentrations of isoflurane were adjusted to 5% initially to achieve this end-tidal concentration as rapidly as possible and were then adjusted using the end-tidal monitor. Respiratory measurements were repeated 30 min after initiation of inhalation anaesthesia.

As secretions in the trachea may affect resistance data, the trachea was suctioned 1 min before every *R*rs measurement to remove any sputum that might influence the resistance measurement. Suctioning was performed with a 10-ml sputum trap attached between the suction catheter and the vacuum source. The total volume of mucus collected during the study was used to categorize patients *post hoc* into two groups: mucus producers (>1 ml) and non-mucus producers (<1 ml).

STATISTICAL ANALYSIS

Comparisons of differences between groups were made using the two-tailed Student's *t* test for unpaired data. Comparisons within groups between different times were made using analysis of variance (ANOVA) and comparisons within subgroups at different times using the Student's *t* test for paired data and Bonferroni's correction to identify specific differences. $P<0.05$ was considered significantly different.

Results

Patients were allocated randomly to one of two groups: propofol ($n=19$, mean age 29 (range 20–45) yr) and thiopentone ($n=18$, mean age 33 (20–49) yr) (table 1). Patients with a history of pre-existing chest disease were excluded. There was no correlation between mucus production and smoking.

Two and 5 min after intubation, *R*rs values were 8.5 (SD 1.5) cm H_2O litre^{-1} s^{-1} and 8.5 (1.4) cm H_2O litre^{-1} s^{-1} in the propofol group, respectively, but 10.9 (3.2) cm H_2O litre^{-1} s^{-1} and 11.0 (3.4) cm H_2O litre^{-1} s^{-1} in the thiopentone group (fig. 1) ($P<0.01$, Student's *t* test for the effect of the drug).

Thirty minutes after initiation of isoflurane–nitrous oxide anaesthesia, *R*rs had declined significantly (to 8.6 (SEM 1.3) cm H_2O litre^{-1} s^{-1}; $P<0.001$, Student's *t* test paired data comparing *R*rs after intubation and 30 min after inhalation anaesthesia) by a mean of 17.5 (3.6) % in the thiopentone group ($P<0.01$) compared with after intubation, but had declined (to 8.3 (1.0) cm H_2O litre^{-1} s^{-1} ; $P<0.002$, Student's *t* test) by only 1.6 (2.6) % in the propofol group (fig. 2) ($P<0.001$ for percentage decline of thiopentone *vs* propofol). *R*rs in the propofol group 30 min after initiation of inhalation anaesthesia did not differ from *R*rs after intubation.

In our 37 patients there was a clear difference in *R*rs between mucus and non-mucus producers. *R*rs

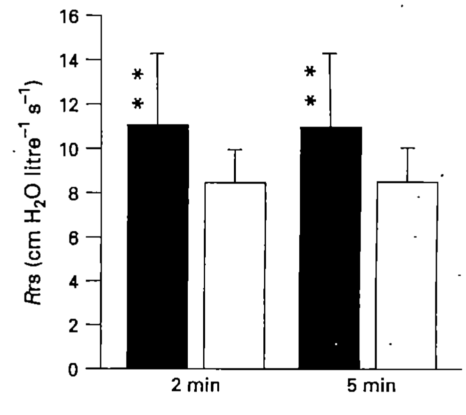

Figure 1 Total respiratory system resistance (*R*rs) at 2 and 5 min after tracheal intubation using thiopentone (■) or propofol (□) for induction of anaesthesia (mean, SD). $^{**}P<0.01$ *vs* propofol.

Table 1 Patient data (mean (SD or range)). No significant differences between groups

	Subgroups					
	Mucus producers			Non-mucus producers		
Group	No of patients	Age (yr)	Weight (kg)	No of patients	Age (yr)	Weight (kg)
Thiopentone	7 (5 male; 3 smokers)	37.5 (26–49)	72.5 (4.4)	11 (10 male; 6 smokers)	30.7 (20–47)	65.9 (6.8)
Propofol	5 (5 male; 4 smokers)	33.8 (24–45)	64.4 (8.7)	14 (12 male; 5 smokers)	27.9 (20–38)	67.8 (7.1)

Table 2 Respiratory system resistance (*R*rs) 5 min after intubation and 30 min after initiation of inhalation anaesthesia in mucus and non-mucus producers in the thiopentone and propofol groups (mean (SD)). **($P<0.01$) compared with *R*rs 5 min after intubation; ††($P<0.01$) compared with non-mucus producers

Group	Number of patients	*R*rs at 5 min post-intubation (cm H_2O litre^{-1}s^{-1})	*R*rs at 30 min after initiation of inhalation anaesthesia (cm H_2O litre^{-1}s^{-1})
Thiopentone			
Mucus producers	7	14.4 (2.1)††	9.7 (1.3)**††
Non-mucus producers	11	8.6 (0.5)	7.9 (0.6)**
Propofol			
Mucus producers	5	10.2 (2.0)††	8.7 (0.9)**††
Non-mucus producers	14	8.0 (0.8)	8.1 (1.0)

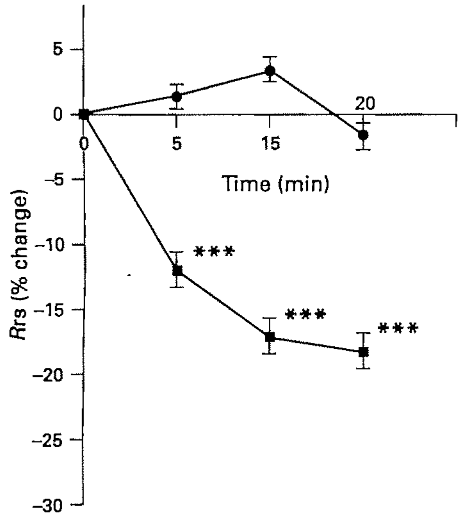

Figure 2 Percentage change in total respiratory system resistance (*R*rs) from baseline (5 min after intubation) to 5, 15 and 30 min after initiation of 1.3% end-tidal isoflurane–50% nitrous oxide after induction of anaesthesia with thiopentone (■) and propofol (●) (mean, SEM). ***$P<0.001$ *vs* propofol.

of mucus producers was significantly higher than non-mucus producers (Student's *t* test for unpaired, $P<0.01$) (table 2). *R*rs values were consistently high regardless of sputum volume among mucus producers suggesting that mucus production is a marker for hyper-reactivity in our patients.

Analysis of the subgroups, mucus *vs* non-mucus producers, demonstrated that propofol and thiopentone mucus producers had significantly higher *R*rs values at both 5 min after intubation and 30 min after initiation of inhalation anaesthesia than non-mucus producers. A significant reduction in *R*rs 30 min after initiation of inhalation was noted for thiopentone and propofol mucus producers together, in addition to thiopentone non-mucus producers, but not for propofol non-mucus producers.

For mucus and non-mucus producers, *R*rs 30 min after administration of the inhalation agent was not different between thiopentone and propofol.

Discussion

The important findings of this study were that compared with thiopentone, propofol attenuated the intubation-induced bronchoconstrictive response. Mucus production was a marker of airway reactivity. In patients with normal airways, propofol provided protection against the intubation-induced bronchoconstrictive response equivalent to 30 min administration of end-tidal 1.3% isoflurane–50% nitrous oxide anaesthesia. In mucus-producing patients however, propofol did not provide full protection but was still better than thiopentone.

We chose to use vecuronium because of the lack of histamine release,[18] and the lack of drug interaction between vecuronium and propofol.[19]

The isovolume method of measuring respiratory resistance used in this study includes the resistance of the tracheal tube. At the flow rates used with a 7.5-mm tracheal tube, this would have resulted in a consistent overestimation of resistance of approximately 4 cm H_2O litre^{-1} s^{-1}.[14] While the exact effect of the tracheal tube on the value depends on expiratory flows and would vary slightly from patient to patient, inter-patient variation would be very small. If the value of 4 is subtracted from all patients, the mean values for the propofol and thiopentone groups become 5 and 7 cm H_2O litre^{-1} s^{-1}, suggesting an approximate 40% increase in resistance if thiopentone is used for induction.

Although the Bicore pulmonary function monitor provides measurements of the resistance of the lung (R_L), *R*rs was used to study the response because of its reproducibility and simplicity of measurement, requiring only airway pressure and flow data. Supine position may influence oesophageal pressure readings and decrease accuracy, and technical difficulties because of oesophageal secretions and catheter movement may make measurements of R_L less reproducible. Under anaesthesia and neuromuscular paralysis, there is a correlation of 0.9998 between R_L and *R*rs in rabbits.[20] Given the inherent difficulties of the oesophageal catheter, *R*rs provides more reliable data. Therefore, we left the oesophageal catheter port of the Bicore open to air so that we measured *R*rs.

Our results suggesting a beneficial effect of propofol on the airways are consistent with several recent studies. Pizov and co-workers showed that the incidence of wheezing was significantly greater in asthmatic patients receiving a barbiturate for induction of anaesthesia than in patients receiving propofol.[13] However, they made no measurement of respiratory resistance. Cigarini and colleagues demonstrated that propofol prevented fentanyl-induced bronchoconstriction in surgical patients.[21] Pederson anecdotally reported that sedative doses of propofol inhibited postoperative bronchospasm in two patients with hyper-reactive airway disease.[22] Prien demonstrated that moving patients from the supine to the lithotomy position, airway impedance was unchanged for patients anaesthetized with propofol, but it increased significantly for patients anaesthetized with thiopentone.[23] Our objective findings after airway stimulation provide further evidence of a protective effect of propofol.

A secondary finding of the study was that a subgroup of patients had significant mucus production after intubation, and that the greatest increase in respiratory resistance occurred in this group of patients. Our finding agrees with others as mucus production has been shown previously to be a marker of airway irritation.[24] Production of 1 ml represents 10% of the normal daily production of the airways and appears to have been a marker for patients with more reactive airways. Among mucus producers, *R*rs 5 min after intubation was significantly higher in the thiopentone group than in the propofol group suggesting that propofol is significantly better than thiopentone in providing protection against the increase in airway resistance in these patients with more reactive airways.

Our finding that there was no correlation between mucus production and smoking agrees with the results in our previous study on the effects of fenoterol on the airway resistance response to tracheal intubation.[25]

Inhalation anaesthetics have been shown to cause bronchodilatation in a dose-related manner.[26 27] Our results in the thiopentone mucus and non-mucus producers confirmed this effect. The addition of end-tidal concentrations of 1.3% isoflurane–50% nitrous oxide after propofol produced a further slight decrease in the mucus producers (significant difference P=0.049 for two-tailed and 0.025 for one-tailed), but not in the non-mucus producers, suggesting that propofol provides bronchodilatation almost equivalent to that provided by inhalation anaesthetics. However, as the number of mucus producers studied was relatively small, interpretation of the decrease in *R*rs 30 min after inhalation anaesthesia for the propofol mucus producers must be made with caution. The magnitude of the additional bronchodilatation after isoflurane was relatively small, implying that even in mucus producers, propofol produced substantial protection.

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References

1. Kil HK, Rooke GA, Ryan-Dykes MA, Bishop MJ. Effect of prophylactic bronchodilator treatment on lung resistance after tracheal intubation. *Anesthesiology* 1994; **81**: 43–48.
2. Gal TJ. Pulmonary mechanics in normal subjects following endotracheal intubation. *Anesthesiology* 1980; **52**: 27–35.
3. Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: A closed claims analysis. *Anesthesiology* 1990; 72: 828–833.
4. Adriani J, Rovenstein EA. The effect of anaesthetic drugs upon bronchi and bronchioles of excised lung tissue. *Anesthesiology* 1943; 4: 253–262.
5. Gold MI, Helrich M. A study of complications related to anesthesia in asthmatic patients. *Anesthesia and Analgesia* 1963; **42**: 283–293.
6. Clarke RSJ, Dundee JW, Garrett RT, McArdle GK, Sutton JA. Adverse reactions to intravenous anaesthetics. *British Journal of Anaesthesia* 1975; **47**: 575–585.
7. Bernstine ML, Berker E, Cullen M. The bronchomotor effects of certain intravenous barbiturates on vagal stimulation in dogs. *Anesthesiology* 1957; **18**: 866–870.
8. Gold MI. Bronchospasm and asthma in the anesthetized patient. *ASA Annual Refresher Course Lectures* 1983; **201**: 242–248.
9. Thompson MC, Davies C. Coughing and bronchospasm with propofol. *Anaesthesia* 1990; **45**: 690–691.
10. Stark RD, Binks SM, Durka VN, O'Connor KM, Arnstein MJA, Glen JB. A review of the safety tolerance of propofol ('Diprivan'). *Postgraduate Medical Journal* 1985; **61** (Suppl. 3):152–156.
11. Mehr EH, Lindeman KS. Effects of halothane, propofol, and thiopental on peripheral airway reactivity. *Anesthesiology* 1993; **79**: 290–298.
12. Cheng EY, Mazzeo AJ, Bosnjak ZJ, Coon RL, Kampine JP. Direct relaxant effects of intravenous anesthetics on airway smooth muscle. *Anesthesia and Analgesia* 1996; **83**: 162–168.
13. Pizov R, Brown RH, Weiss YS, Baranov D, Hennes H, Baker S, Hirshman CA. Wheezing during induction of general anesthesia in patients with and without asthma. *Anesthesiology* 1995; **82**: 1111–1116.
14. Wright PE, Marini JJ, Bernard GR. In vitro and in vivo comparison of endotracheal tube airflow resistance. *American Review of Respiratory Disease* 1989; **140**: 10–16.
15. Petros AJ, Lamond CT, Bennett D. The Bicore pulmonary monitor. *Anaesthesia* 1993; **48**: 985–988.
16. Yamazaki Y, Yamakage M, Ujike Y, Namiki A. Changes in work of breathing during continuous positive airway pressure with increased airway resistance. *Chest* 1994; **105**: 860–867.
17. Nathan SD, Ishaaya AM, Koerner SK, Belman MJ. Prediction of minimal pressure support during weaning from mechanical ventilation. *Chest* 1993; **103**: 1215–1219.
18. Vettermann J, Beck KC, Sten GE, Lindahl SGE, Brichant JF, Rehder K. Actions of enflurane, isoflurane, vecuronium, atracurium, and pancuronium on pulmonary resistance in dogs. *Anesthesiology* 1988; **69**: 688–695.
19. McCarthy GJ, Mirakhur RK, Pandit SK. Lack of interaction between propofol and vecuronium. *Anesthesia and Analgesia* 1992; **75**: 536–538.
20. Wu SC, Hildebrandt J, Isner PD, Pierson DJ, Bishop MJ. Efficacy of anticholinergic and beta-adrenergic agonist treatment of maximal cholinergic bronchospasm in tracheally intubated rabbits. *Anesthesia and Analgesia* 1992; **75**: 777–783.
21. Cigarini I, Bonnet F, Lorino AM, Harf A, Desmonts JM. Comparison of the effects of fentanyl on respiratory mechanics under propofol or thiopental anaesthesia. *Acta Anaesthesiologica Scandinavia* 1990; **34**: 253–256.
22. Pederson CM. The effect of sedation with propofol on postoperative bronchoconstriction in patients with hyperreactive airway disease. *Intensive Care Medicine* 1992; **18**: 45–46.
23. Prien T. Lithotomy position: respiratory resistance with thiopental and propofol anesthesia. *Anasthesiol, Intensivmed, Notfallmed, Schmerzther* 1995; **30**: 20–22.
24. Phipps RJ, Richardson PS. The effects of irritation at various levels of the airway upon tracheal mucus secretion in the cat. *Journal of Physiology (London)* 1976; **261**: 563–581.
25. Wu SC, Wu KC, Tsai YH, Cheng RKS, Tan PPC. Inhaled fenoterol pretreatment attenuates airway resistance response to endotracheal intubation. *Acta Anaesthesiologica Sinica* 1995; **33**: 7–14.
26. Brown RH, Mitzner W, Zerhouni E, Hirshman CA. Direct in vivo visualization of bronchodilation induced by inhalation anesthesia using high resolution computed tomography (HRCT). *Anesthesiology* 1993; **78**: 295–300.
27. Mazzeo AJ, Cheng EY, Stadnicka A, Bosnijak ZJ, Coon RL, Kampine JP. Topographical differences in the direct effects of isoflurane on airway smooth muscle. *Anesthesia and Analgesia* 1994; 78 (5): 948–954.

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Propofol or halothane anaesthesia for children with asthma: effects on respiratory mechanics

W. HABRE, I. MATSUMOTO AND P. D. SLY

Summary

Propofol may cause histamine release and alter airway tone and reactivity. Although its use has been reported to be safe in asthmatics, there is a lack of information on its effect on lung function in children with asthma. We measured respiratory mechanics after i.v. or inhalation anaesthesia in 60 children, aged 2–12 yr, with or without asthma. Anaesthesia was induced with propofol 3 mg kg^{-1}, fentanyl 1 μg kg^{-1} and atracurium 0.5 mg kg^{-1} and maintained with an infusion of propofol 10 mg $kg^{-1}h^{-1}$ and 50% nitrous oxide in oxygen. Halothane was administered subsequently at a concentration of 1 MAC. Respiratory mechanics were measured by applying a single-compartment model using multi-linear regression analysis to calculate dynamic compliance (Crs,dyn) and respiratory system resistance (Rrs), based on: $P\text{ao} = V/C\text{rs,dyn} + \dot{V}\, R\text{rs} + P\text{A,EE}$, where Pao = airway opening pressure, PA,EE = alveolar pressure, V = volume and $\dot{V}$ = flow. The two groups were comparable in age, weight and ventilation variables (tidal volume and peak pressure). Respiratory mechanics during propofol anaesthesia were comparable in normal and asthmatic children (Rrs = 20.5×10^{-4} (SD 5.2×10^{-4}) *vs* 21.5×10^{-4} (5.7×10^{-4}) kPa ml^{-1} s^{-1} (ns) and Crs,dyn = 247.5 (76.5) *vs* 235.1 (63.8) ml kPa^{-1} (ns)). Halothane produced a minimal decrease in Rrs and a minimal increase in tidal volume in both groups without changes in Crs,dyn. In conclusion, respiratory mechanics were comparable after propofol anaesthesia in both children with and without asthma. Changes in Rrs after halothane administration were not clinically relevant. (*Br. J. Anaesth.* 1996; **77**: 739–743)

Key words
Anaesthesia, paediatric. Anaesthetics i.v., propofol. Anaesthetics volatile, halothane. Asthma. Ventilation, mechanics. Lung, mechanics. Lung, function.

With the worldwide increase in the prevalence of asthma[1–3] an increased number of asthmatics are likely to require anaesthesia for surgical procedures. As asthma is characterized by increased airway reactivity to different stimuli, the choice of anaesthetic technique should consider the increased risk of bronchospasm in children with asthma. Anaesthesia may induce changes in airway resistance, alter ventilation distribution, produce atelectasis and reduce lung volume,[4] any of which may result in hypoxaemia.

Propofol has several advantages for use in paediatric anaesthesia. It has been shown to reduce the incidence of airway obstruction at induction,[5] shorten recovery time and allow earlier discharge for outpatients,[6 7] and to reduce postoperative emesis.[8 9] However, propofol has been reported to induce histamine release in healthy[10] and atopic patients.[11] Excessive histamine release may provoke bronchoconstriction in asthmatic patients and would limit its usefulness in this group. While propofol has been reported to be safe in asthmatic patients,[12–14] there is a lack of information on its effect on lung function in asthmatics, particularly children. Objective lung function data are required before recommending the use of propofol in asthmatic children.

This study was designed to measure respiratory mechanics in children with asthma undergoing mechanical ventilation during (i) induction of anaesthesia with propofol and (ii) maintenance of anaesthesia with halothane in children with and without asthma. For practical reasons respiratory mechanics were measured during propofol anaesthesia first, followed by measurements during halothane anaesthesia.

Patients and methods

After obtaining institutional Ethics Committee approval and parental informed consent, we studied 60 children, aged 2–12 yr, undergoing elective surgery requiring general anaesthesia and mechanical ventilation. Based on the medical history during preoperative anaesthetic assessment, children were

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classified as having asthma (children with a history of physician diagnosed asthma, stabilized under medical treatment before undergoing surgery) or not (children with normal lungs and no history of asthma, hay fever or allergies). Children with a history of upper respiratory infection within 4 weeks, and children with acute or chronic respiratory disease other than asthma were excluded.

All children had EMLA cream applied on both hands 1 h before surgery, and received oral midazolam 0.25–0.35 mg kg^{-1}, 30 min before induction of anaesthesia with propofol 3 mg kg^{-1} and fentanyl 1 μg kg^{-1}. Propofol was then continued at a rate of 10 mg kg^{-1} h^{-1} in the presence of 50% nitrous oxide in oxygen while respiratory mechanics were measured. A tracheal tube was inserted after administration of atracurium 0.5 mg kg^{-1}. The size of the uncuffed tracheal tube was chosen to avoid leak at the pressures encountered during mechanical ventilation. If a leak was detected around the tracheal tube, a throat pack was inserted or cricoid pressure was applied, or both, during measurements. The lungs were ventilated mechanically with a volume-controlled ventilator (Air-Shields Ventimeter Controller) and ventilatory frequency was titrated to achieve an end-tidal carbon dioxide concentration of approximately 4.6 kPa. After respiratory measurements were obtained during infusion of propofol, anaesthesia was subsequently maintained with 1% halothane and 50% nitrous oxide in oxygen.

The measurement equipment, consisting of a pressure port and transducer (Microswitch 142 PC01D) to measure airway opening pressure (Pao) and a pneumotach (Hans Rudolph Inc. K.C., MO, USA) to measure flow ($\dot{V}$) was placed between the patient's tracheal tube and the ventilator circuit. Pao and $\dot{V}$ signals were amplified (Applied Measurement, 022A), low- pass filtered (cut-off frequency 10 Hz, Applied Measurement, 043) and stored on computer. All data were collected and analysed using a data acquisition package (Anadat and Labdat, RHT Infodat, Montreal, Canada).

MEASUREMENT OF RESPIRATORY MECHANICS

Respiratory mechanics were measured during mechanical ventilation using well characterized methods.[15 16] Multi-linear regression analysis was used to calculate respiratory system compliance (Crs,dyn) and resistance (Rrs) from measurements of airway opening pressure (Pao), flow ($\dot{V}$) and volume (V) using the equation:

$$Pao = V/Crs,dyn + \dot{V}Rrs + PA,EE \qquad (1)$$

The constant term in equation (1) (PA,EE) reflects alveolar pressure.[17] Data were used only if the coefficient of determination (r^2) of this fit was > 0.98.

CORRECTION FOR GAS PHYSICAL PROPERTIES

Measurements of flow obtained from a pneumotachograph are influenced by the physical properties of the gas passing through. When using gases with different physical properties, one must correct for this effect. We used the principles applied by Johns, Pretto and Streeton[18] to determine the appropriate correction factor for the gas concentrations used in this study. Using a 100-ml syringe filled with the gas mixture used in each part of the study, 100 ml of gas were flushed through the pneumotachograph and the resulting flow integrated to produce a volume measurement. By repeating this manoeuvre 20 times with each gas mixture, the relevant correction factors were calculated and subsequently applied to the flows measured with the relevant gas mixture.

STUDY DESIGN

All measurements were completed in the anaesthetic induction room before surgical stimulation. After tracheal intubation and 5 min of steady state mechanical ventilation during infusion of propofol, a first set of three discrete 20-s epoch measurements were obtained. Infusion of propofol was then discontinued and anaesthesia was maintained with 1% halothane and 50% nitrous oxide in oxygen. An anaesthetic gas analyser (ICOR agent ANM 605) was used to determine when a steady state concentration had been reached. An expiratory halothane concentration of 0.7% (1 MAC) was achieved within 5–8 min. Measurements of respiratory mechanics were then repeated.

STATISTICAL ANALYSIS

A 20% difference in resistance (Rrs) between asthmatic and normal children, or a 20% change in Rrs with anaesthetic were considered clinically significant. Based on the intra-subject variability of Rrs, calculated using the multi-linear regression technique,[15 19] groups of 30 subjects have been shown to have 95% power to detect a 20% difference in Rrs between groups.

Comparisons between asthmatic and normal children were made using the unpaired two-tailed t test. Paired two-tailed t tests were used to compare changes in respiratory mechanics before and after administration of halothane. Statistical significance was accepted at the 5% level. Data analysis was performed using SPSS 6.1 for Windows. Data are presented as mean (SD).

Results

The two groups of patients were comparable in age, weight, sex and size of the tracheal tube (table 1). The different clinical patterns and treatment of asthma are shown in table 2. Seventeen of the asthmatic children had received a bronchodilator on the morning before admission to theatre. There was no significant difference in airway resistance between the asthmatic children who received bronchodilators

Table 1 Patient data (mean (SD) [range]). No significant differences between groups

	Control (n=30)	Asthma (n=30)
Age (months)	75.3 [27–124]	81.1 [22–143]
Weight (kg)	23.9 (7.9) [11.95–38.4]	24.4 (9.5) [10.4–50]
Sex (M/F)	13/17	18/12

Table 2 Individual clinical data for children classified as having asthma. Pattern of asthma is presented as persistent episodes (P), infrequent episodes (I) and seasonal episodes (S). Medical treatment is presented as bronchodilators (B), inhaled steroids (IS), oral steroids (OS) and cromoglycate (C). *Received bronchodilator on the day of surgery

Patient No.	Age (yr mths)	Asthma severity	Treatment	Preoperative bronchodilator
4	4 11	P	B	*
5	8 11	S	B	
8	6 10	S	B	
15	11 9	I	B, IS	*
17	7 1	I	B	
19	2 8	P	B, OS	*
21	7 5	I	B	
23	9 5	S	IS	*
24	5 6	I	B	*
31	4 1	I	B	
34	9 3	P	B, C, IS	*
35	1 10	I	B	*
36	6 5	P	B, IS	*
37	6 8	I	B, IS	*
38	3 10	I	B, IS	
39	3 10	S	B	
40	11 10	I	B	
41	4 9	S	B, IS, C	*
42	4 4	P	B	
43	7 7	P	B, C	*
44	6 10	I	B	
45	7 7	P	B, IS	*
48	9 9	I	B, IS	
49	3 5	P	B	
51	10 1	I	B	
52	8 10	P	B, IS	*
53	5 1	P	B, C	*
54	8 8	P	B, IS	*
59	9 6	I	B, IS	*
60	4 3	P	B, C	*

and those who did not (22.6×10^{-4} (SD 5.6×10^{-4}) *vs* 20.2×10^{-4} (5.7×10^{-4}) kPa ml^{-1} s^{-1}).

Ventilation variables were comparable between the groups. With the ventilator set to achieve an end-tidal carbon dioxide concentration of approximately 4.6 kPa, the lungs of the children were ventilated with a tidal volume of approximately 10 ml kg^{-1} and a frequency of 0.25 Hz, with an inspiratory–expiratory time ratio of 0.5 (table 3). There

Table 3 Ventilation variables measured 5 min after tracheal intubation during propofol infusion for maintenance of anaesthesia (mean (SD)). No significant difference between groups

	Control	Asthma
Tidal volume (ml kg^{-1})	10.85 (2.14)	10.65 (2.64)
Frequency (Hz)	0.25 (0.02)	0.25 (0.03)
T_I/T_E	0.55 (0.15)	0.50 (0.14)
Peak pressure (kPa)	1.84 (0.22)	1.91 (0.26)
End-expiratory pressure (kPa)	0.29 (0.14)	0.25 (0.07)

were no significant differences between the two groups in airway pressure (peak pressure, mean pressure and end-expiratory pressure) and respiratory mechanics (dynamic compliance and resistance) (table 4).

During administration of halothane, in both groups there was a significant increase in tidal volume and a decrease in *R*rs, while *C*rs,dyn did not change (table 4). Both of these changes were small and not clinically significant. Furthermore, changes in tidal volume and respiratory mechanics were equivalent in both groups before and after administration of halothane. The decrease in airway resistance was comparable in asthmatic patients who had received bronchodilators in the morning and those who had not (7.4×10^{-4} (1.3×10^{-4}) *vs* 5.8×10^{-4} (1.2×10^{-4}) kPa ml^{-1} s^{-1}).

Discussion

We have found that respiratory mechanics were comparable in asthmatic and non-asthmatic children after induction of anaesthesia with propofol. Furthermore, changes during halothane anaesthesia were not clinically significant suggesting that propofol was not associated with any adverse effects in children with or without asthma.

This study provides information on respiratory mechanics in children with and without asthma, receiving routine induction of anaesthesia with propofol, followed by maintenance with halothane. This anaesthetic regimen mimics that which would

Table 4 Changes in ventilation variables and respiratory mechanics before and after halothane administration. Changes in ventilation parameters and respiratory mechanics before and after administration of halothane (mean (SD) [range]). $*P < 0.05$

	Control	Asthma
Tidal volume (ml)		
Propofol	248 (60) [134–352]	244 (58) [98–371]
Halothane	252 (62)* [136–371]	248 (59)* [98–380]
Peak pressure (kPa)		
Propofol	1.84 (0.22) [1.3–2.3]	1.91 (0.26) [1.5–2.6]
Halothane	1.89 (0.23) [1.33–2.35]	1.93 (0.24) [1.6–2.4]
Mean airway pressure (kPa)		
Propofol	0.55 (0.13) [0.38–0.96]	0.49 (0.08) [0.4–0.79]
Halothane	0.59 (0.17) [0.41–1]	0.51 (0.08) [0.42–0.86]
Compliance (ml kPa^{-1})		
Propofol	247.5 (76.5) [120–431]	235.1 (63.8) [116–352]
Halothane	248.9 (81) [116–461]	235.8 (63.2) [114–363]
Resistance (kPa ml^{-1} s^{-1})		
Propofol	20.5×10-4 (5.2×10^{-4}) $[12.15–31.7]\times10^{-4}$	21.5×10^{-4} (5.7×10^{-4}) $[14.3–36.3]\times10^{-4}$
Halothane	20.1×10^{-4} (5.1×10^{-4})* $[12–31]\times10^{-4}$	20.9×10-4 (5.0×10^{-4})* $[14.2–33.7]\times10^{-4}$

be used clinically in children, if propofol was shown to be safe in children with asthma. Ideally, we would have wished to obtain measurements of respiratory mechanics before and after propofol and before and after halothane. This design is impractical as propofol is given to induce anaesthesia. If anaesthesia was induced with a volatile agent, such as halothane, the presence of this agent would be likely to mask any changes caused by propofol. In addition, the design used in this study mimics the clinical situation in which these drugs are used. To circumvent our inability to measure respiratory mechanics before and after introduction of propofol, we compared results obtained in asthmatic and non-asthmatic children and after achieving a concentration of 1 MAC of halothane. If propofol produced bronchospasm in children, we would have expected to see a significant decrease in *R*rs after introduction of halothane. Similarly, if propofol had more adverse effects in asthmatic children, we would have expected to find a higher resistance in this group compared with the control, and a bronchodilator response with halothane. Neither of these patterns was seen.

Some reports have suggested that propofol causes histamine release in healthy[10] and atopic patients,[11] and may induce bronchospasm.[20 21] To our knowledge, there are no reports of respiratory mechanics after propofol anaesthesia in children. In this study, *R*rs was slightly higher in asthmatic children and this difference was found at all stages of the study but was not statistically significant. The difference in group means was small ($< 1.0 \times 10^{-4}$ kPa ml^{-1} s^{-1}) and not clinically significant. *C*rs,dyn was also slightly lower in the asthmatic group. These differences may have resulted from either differences in baseline lung function or greater propofol-induced histamine release in asthmatic children. In both cases the differences were too small to be considered important and suggest that the use of propofol is safe in children with asthma.

It has also been suggested that propofol causes greater bronchospasm when combined with another histamine-releasing substance such as atracurium,[22] which can induce histamine-release from mast cells.[23] All children in this study received propofol and atracurium at induction of anaesthesia. If histamine release was a significant clinical problem with either or both of these drugs, we might have expected a greater effect in asthmatic children as airway sensitivity to histamine is increased in asthmatics.[24] However, we did not observe any significant differences in ventilation variables or in respiratory mechanics between the two groups of children. These findings support a recent study in which it was found that atracurium 0.5 mg kg^{-1} had no clinically significant effects on the airways.[25]

Halothane produced small but consistent bronchodilatation in both groups and the decrease in *R*rs was similar in children with and without asthma. Previous studies have shown that halothane reduces airway resistance, primarily when increased by chemical agonists.[26 27] Most recently, 1 MAC of halothane has been found to dilate the airways of normal canine lungs without preconstriction.[28] These authors also showed that halothane does not exert any effect on lung tissue mechanical properties. While one must always be cautious in extrapolating data from animal studies to humans, our results are consistent with these findings as our single compartment model was sensitive enough to detect a mild but statistically significant decrease in *R*rs without any change in *C*rs,dyn. The decrease in *R*rs contributed to the mild increase in tidal volume which was not clinically significant.

While no changes in group mean lung function occurred, to ensure that no clinically important subgroup was missed, we examined the magnitude of the reductions in resistance occurring in individual children. A 10% decrease in resistance is the minimum that would be considered clinically significant and is well beyond the variability of our measurements. One non-asthmatic and four asthmatic children showed a reduction in resistance of 10% or more after introduction of halothane and no child had a change of 20%, demonstrating that the changes in resistance were not clinically significant.

In interpreting our data one must realize that we do not have measurements of absolute lung volume. If propofol caused bronchoconstriction this could be accompanied by an increase in functional residual capacity (FRC) (or less decrease in FRC than is usually produced by induction of anaesthesia). Under these circumstances the introduction of halothane would be expected to produce bronchodilatation and a reduction in FRC to the normal (anaesthetic) baseline. As airway resistance is volume-dependent, a decrease in FRC may result in an increase in resistance, masking the bronchodilator effect of halothane. We do not believe this possible scenario can explain our data for the following reason. As part of our multi-linear regression analysis of lung function, we produced a value for end-expiratory alveolar pressure (*P*A,EE in equation (1)). This measurement has been validated against direct measurements of alveolar pressure in animals.[17] End-expiratory alveolar pressure is determined by the elastic recoil of the lungs and chest wall at the absolute lung volume at which end-expiration occurs and by any externally applied positive end-expiratory pressure (provided sufficient expiratory time has been allowed for the lungs to empty to their "resting" volume). Thus *P*A,EE is dependent on absolute lung volume and can be used as a surrogate marker of end-expiratory lung volume, provided respiratory system compliance does not change. In this study, compliance did not change with the introduction of halothane and the mean change in *P*A,EE was 0.039 kPa for the non-asthmatic group and 0.017 kPa for asthmatics. These data strongly suggest that a change in lung volume did not occur with the introduction of halothane and that this potential confounder is not the reason that we did not see a significant reduction in airway resistance with halothane.

Among the different techniques used to measure dynamic respiratory mechanics that have been validated for use in children during anaesthesia, multiple linear regression techniques (MLR) are the most easily implemented.[15 16 19] During ventilation, MLR uses measurements of *Pao*, $\dot{V}$ and *V* throughout the entire respiratory cycle to calculate *Crs*,dyn and *Rrs*. We achieved consistently a good fit during mechanical ventilation ($r^2 > 0.98$). This good coefficient of determination suggests that the application of the single-compartment model for measurements of dynamic mechanics in our study is a good approximation of the mechanical properties of the respiratory system ventilated at a single frequency.

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References

1. Carman PG, Landau LI. Increased paediatric admissions with asthma in Western Australia—a problem of diagnosis? *Medical Journal of Australia* 1990; **152**: 23–26.
2. Weitzman M, Gortmaker SL, Sobol AM, Perrin JM. Recent trends in the prevalence and severity of childhood asthma. *Journal of the American Medical Association* 1992; **268**: 2673–2677.
3. Erzen D, Roos LL, Manfreda J, Anthonisen NR. Changes in asthma severity in Manitoba. *Chest* 1995; **108**: 16–23.
4. Hirshman CA, Bergman NA. Factors influencing intra pulmonary airway calibre during anaesthesia. *British Journal of Anaesthesia* 1990; **65**: 30–42.
5. Martin TM, Nicolson SC, Bargas MS. Propofol anesthesia reduces emesis and airway obstruction in pediatric outpatients. *Anesthesia and Analgesia* 1993; **76**: 144–148.
6. Hannallah RS, Britton JT, Schafer PG, Patel RI, Norden JM. Propofol anaesthesia in paediatric ambulatory patients: a comparison with thiopentone and halothane. *Canadian Journal of Anaesthesia* 1994; **41**: 12–18.
7. Runcie CJ, Mackenzie SJ, Arthur DS, Morton NS. Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone. *British Journal of Anaesthesia* 1993; **70**: 192–195.
8. Reimer EJ, Montgomery CJ, Bevan JC, Merrick PM, Blackstock D, Popovic V. Propofol anaesthesia reduces early postoperative emesis after paediatric strabismus surgery. *Canadian Journal of Anaesthesia* 1993; **40**: 927–933.
9. Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. *Anesthesiology* 1991; **75**: 204–209.
10. Doenicke A, Lorenz W, Stanworth D, Duka TH, Glen JB. Effects of propofol ('Diprivan') on histamine release, immunoglobulin levels and activation of complement in healthy volunteers. *Postgraduate Medical Journal* 1985; **61** (Suppl.3): 15–20.
11. Laxenaire MC, Mata E, Guéant JL, Moneret-Vautrin DA, Haberer JP. Basophil histamine release in atopic patients after *in vitro* provocation with thiopental, Diprivan and chlormethiazole. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 706–710.
12. Bibault P, Boisson-Bertrand D, Duvivier C, Peslin R, Laxenaire MC. Effect of the association propofol–alfentanil on bronchial resistances in asthmatic patients. *Annales Françaises d'Anesthésie et de Réanimation* 1991; **10**: 264–268.
13. Clarkson K, Power CK, O'Connell F, Pathmakanthan S, Burke CM. A comparative evaluation of propofol and midazolam as sedative agents in fiberoptic bronchoscopy. *Chest* 1993; **104**: 1029–1031.
14. Pizov R, Brown RH, Weiss YS, Baranov D, Hennes H, Baker S, Hirshman CA. Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. *Anesthesiology* 1995; **82**: 1111–1116.
15. Lanteri CJ, Sly PD. Changes in respiratory mechanics with age. *Journal of Applied Physiology* 1993; **74**: 369–378.
16. Lanteri CJ, Kano S, Nicolai T, Sly PD. Measurement of dynamic respiratory mechanics in neonatal and pediatric intensive care: the multiple linear regression technique. *Pediatric Pulmonology* 1995; **95**: 29–45.
17. Nicolai T, Lanteri C, Freezer N, Sly PD. Non-invasive determination of alveolar pressure during mechanical ventilation. *European Respiratory Journal* 1991; **4**: 1275–1283.
18. Johns DP, Pretto JJ, Streeton JA. Measurement of gas viscosity using a standard Fleisch pneumotachograph. *Journal of Applied Physiology* 1982; **53**: 290–293.
19. Sly PD, Bates JHT. Computer analysis of physical factors affecting the use of interrupter technique in infants. *Pediatric Pulmonology* 1988; **4**: 219–224.
20. Watkins J. Second report from an anaesthetic reactions advisory service. *Anaesthesia* 1989; **44**: 157–159.
21. Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, Guéant JL. Life-threatening anaphylactoid reactions to propofol (Diprivan). *Anesthesiology* 1992; **77**: 275–280.
22. Naquib M. Anaphylactoid reactions following propofol–atracurium sequence. *Canadian Journal of Anaesthesia* 1989; **36**: 358–359.
23. North FC, Kettelkamp N, Hirshman CA. Comparison of cutaneous and in vitro histamine release by muscle relaxants. *Anesthesiology* 1987; **66**: 543–546.
24. Woolcock AJ, Salome CM, Yan K. The shape of the dose–response curve to histamine in asthmatic and normal subjects. *American Review of Respiratory Disease* 1984; **130**: 71–75.
25. Mehr EH, Hirshman CA, Linderman KS. Mechanism of action of atracurium on airways. *Anesthesiology* 1992; **76**: 448–454.
26. Shah MV, Hirshman CA. Mode of action of halothane on histamine-induced airway constriction in dogs with reactive airways. *Anesthesiology* 1986; **65**: 170–174.
27. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalation anesthesia on airways. *Anesthesiology* 1982; **56**: 107–111.
28. Sato J, Shinozuka N, Kochi A, Ushida H, Mizugushi T. Low-dose halothane produces airway dilatation but does not alter parenchymal mechanics in the normal canine lung. *Canadian Journal of Anaesthesia* 1995; **42**:438–445.

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Hepatocellular integrity during and after isoflurane and halothane anaesthesia in surgical patients

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Summary

Subclinical disturbance in hepatocellular integrity, indicated by glutathione transferase Alpha (GSTA), has been associated with halothane, sevoflurane and propofol, but not with isoflurane anaesthesia. We anaesthetized 82 patients with isoflurane or halothane at 1 MAC for superficial surgery. GSTA concentration were measured with a sensitive time-resolved immunofluorometric assay in serum samples. GSTA concentrations increased from a baseline value of geometric mean 1.8 μg litre^{-1} (95% confidence intervals 1.4–2.2 μg litre^{-1}) to a peak of 4.3 (3.3–5.7) μg litre^{-1} in the isoflurane group and from 2.1 (1.6–2.9) μg litre^{-1} to 6.2 (4.1–9.5) μg litre^{-1} in the halothane group. The change in GSTA was significant within groups but the difference between groups was not significant. Two patients exhibited an unexpectedly large increase in GSTA (peaks 370 and 620 μg litre^{-1}) and a mild increase in alanine aminotransferase after halothane anaesthesia. We conclude that hepatocellular integrity was mildly disturbed after isoflurane and halothane anaesthesia but there was no difference between anaesthetics. Halothane anaesthesia may be associated with more advanced hepatocellular disturbance in some cases. (*Br. J. Anaesth.* 1996; **77**: 744–747)

Key words
Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Enzymes, glutathione transferase. Liver, function. Liver, hepatotoxicity.

Disturbance in hepatocellular integrity indicated by a sensitive marker, glutathione transferase Alpha (GSTA), has been noted after halothane,[1–3] sevoflurane[3] and propofol[4] anaesthesia, but not after isoflurane anaesthesia.[1 2] There is some disagreement between studies which used an enzyme immunoassay or a time-resolved immunofluorometric assay for GSTA measurements after sevoflurane[3 5] and propofol[4 6] anaesthesia. For example, the enzyme immunoassay kit does not appear to be sensitive enough to detect small changes in serum concentrations of GSTA.[7] In addition, because of the relatively short half-life of GSTA in serum (56 min),[8] GSTA should be assayed in samples collected at short intervals. This has not been the case in several recently published studies involving anaesthesia and GSTA where no samples were obtained for several hours after the end of anaesthesia.[2 5 6] Therefore, we have attempted to confirm the reported differential influence of isoflurane and halothane anaesthesia on hepatocellular integrity by using a new, sensitive, time-resolved immunofluorometric assay for GSTA[9] and short sampling intervals.

Patients and methods

The study was approved by the Ethics Committee of the Surgical Hospital, Helsinki University Central Hospital. Informed consent was obtained from all patients. We studied 82 patients, aged 22–64 yr, with a body mass index (BMI) <30 kg m^{-2} (weight × height^{-2}) undergoing superficial surgery during general anaesthesia lasting at least 2 h (table 1). Exclusion criteria were patients with known liver disease or a history of heavy alcohol consumption, those with hyperthyroidism or receiving thyroxine medication, those receiving medication likely to affect the liver, and those who were suspected to have had an adverse anaesthesia-related effect after a previous inhalation anaesthetic. Administration of paracetamol or corticosteroids was not allowed within 3 days before or during the study.

Patients were allocated randomly to one of two groups of 41 patients each, to receive either isoflurane or halothane anaesthesia. Premedication comprised oral diazepam, approximately 0.2 mg kg^{-1}. Glycopyrronium 0.2 mg, fentanyl 3 μg kg^{-1}, thiopentone 3–6 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} were given during induction of anaesthesia. After tracheal intubation, normocapnia was maintained with mechanical ventilation using oxygen-enriched air ($F\text{I}_{O_2}$=0.35) without positive end-expiratory pressure. Anaesthesia was maintained with isoflurane at an expiratory concentration of 0.8%, which was 0.68 (SD 0.04) MAC (age-corrected mean) or 0.5% halothane, which was 0.65 (0.03) MAC, for 30 min. Thereafter, isoflurane was maintained at 1.2%

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(1.02 (0.05) MAC) or 0.75% halothane (0.98 (0.04) MAC), until the end of anaesthesia. Small increments of fentanyl 0.05–0.1 mg were given if heart rate or arterial pressure increased. Nitrous oxide (FI_{N_2O}=0.65) was added if a patient expressed clinical signs of inadequate anaesthesia after fentanyl increments. If neuromuscular block was needed, it was maintained with increments of vecuronium 1 mg and antagonized with neostigmine 2 mg and glycopyrronium 0.4 mg. Inspiratory and expiratory concentrations of isoflurane and halothane were monitored continuously (Capnomac Ultima, Datex, Helsinki, Finland). Other monitoring included non-invasive arterial pressure every 5 min and continuous electrocardiography, pulse oximetry, and inspiratory and expiratory P_{O_2} and P_{CO_2} (Capnomac Ultima and Cardiocap, Datex, Helsinki, Finland). Haemodynamic state was characterized by calculating the mean of systolic arterial pressure and heart rate during anaesthesia. The threshold of hypotension was defined as systolic arterial pressure 85 mm Hg, and the degree of hypotension was calculated as the area under the curve (AUC) of hypotension. Hypotension was defined as an AUC value of >100 mm Hg min. Hypotension was managed by increasing the rate of fluid administration and if nitrous oxide was administered, it was discontinued (two patients in each group). After anaesthesia, patients were observed for 3 h in the post-anaesthesia care unit and thereafter on the ward. After operation, oxycodone 0.07 mg kg^{-1} i.v. or 0.14 mg kg^{-1} i.m. was given when a patient requested pain medication.

SAMPLES AND LABORATORY ANALYSIS

Peripheral venous blood was obtained before anaesthesia (baseline), hourly during anaesthesia, and 0, 1, 3, 6 and 24 h after the end of anaesthesia. Serum was stored at −20 °C, that is at a temperature which we have found to conserve the antigenic integrity of GSTA for an immunoassay.

GSTA concentrations were measured with a time-resolved immunofluorometric assay according to a standard assay procedure, except that the Eu^{3+} label was incubated for 3 h.[9] Samples from each patient were analysed in one assay cycle. The detection limit of the assay was 0.03 μg litre^{-1} and the measuring range was 0.3−1000 μg litre^{-1} at 10-fold serum dilution. Mean intra-assay and inter-assay coefficients of variation (CV) were 4.5–5.4% and 11.3–17.0%, respectively.[7] The reference ranges of GSTA were 0.7–6.0 μg litre^{-1} and 0.7–14 μg litre^{-1} for females and males, respectively.[9]

Baseline concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transferase and bilirubin were measured in routine hospital laboratory tests in serum samples obtained before anaesthesia. The detection limits for AST and ALT were less than 5 iu litre^{-1} and the inter-assay CV was 2.2–3.6%. ALT and AST were also measured 24 h after the end of anaesthesia.

STATISTICAL ANALYSIS

The skewed distributions of GSTA concentrations and aminotransferase activities were normalized by logarithmic transformation. Changes were compared between groups and at successive times using repeated measures analysis of variance (ANOVA). Student's *t* test was used for comparison of the peak and area under the concentration curve (AUC) values between the groups on a logarithmic scale. Systat software was used in computing.[10] For power analysis, GSTA concentration >66% above or >40% below the reference was considered as clinically significant, that is 0.22 on $\log_{10}$ scale. The SD values of GSTA concentrations were predicted to be 0.3 on $\log_{10}$ scale. Forty-one patients in both groups were required for a power of 90% at α=0.05 or 36 patients for 85%, respectively.[11]

Results

Results from 75 patients were analysed (38 in the isoflurane group and 37 in the halothane group). Six patients were excluded because the baseline GSTA concentration was higher than the upper limit of the reference range, and one patient because she underwent re-operation because of bleeding. Patients in the isoflurane and halothane groups were comparable in sex distribution, age, height, weight, BMI, type of surgery and incidence of malignancy (table 1). Peroperative bleeding was 500 ml or less, except in four patients in the isoflurane group (600–1100 ml) and in five patients in the halothane group (600–1600 ml). Duration of anaesthesia and need for fentanyl, nitrous oxide, vecuronium and neostigmine were similar in both groups (table 2). Mean values for arterial pressure were the same in both

Table 1 Patient characteristics and type of surgery (mean (SD or range) or number). Body mass index (BMI)=weight × height^{-2}

	Isoflurane (*n*=38)	Halothane (*n*=37)
Sex (M/F)	9/29	12/25
Age (yr)	41 (22–64)	42 (25–58)
Height (cm)	169 (8.7)	169 (9.3)
Weight (kg)	66 (10.5)	68 (9.6)
BMI (kg m^{-2})	23.2 (2.3)	23.8 (2.5)
Type of surgery		
Mammary gland	19	19
Thyroid gland	11	7
Male genital	8	11
Malignancy		
Mammary gland	13	10
Thyroid gland		1

Table 2 Anaesthesia characteristics (mean (SD) or number). *(*P*<0.05) between groups

	Isoflurane (*n*=38)	Halothane (*n*=37)
Duration of anaesthesia (min)	190 (70)	194 (54)
Thiopentone (mg)	349 (98)	358 (108)
Fentanyl (mg)	0.38 (0.13)	0.41 (0.17)
Vecuronium (mg)	11.9 (4.1)	11.9 (4.3)
Nitrous oxide (No. of patients)	6	8
Neostigmine (No. of patients)	16	16
Haemodynamics during anaesthesia		
Mean systolic arterial pressure (mm Hg)	100.8 (6.4)	101.8 (7.1)
Mean heart rate (beat min^{-1})	71.3 (10.1)*	66.5 (7.5)*
Hypotensive patients (*n*)	7	8

Table 3 GSTA concentrations (µg litre^{-1}) in serum and area under the concentration curve (AUC) values (geometric mean (95% confidence interval)). Significant differences compared with baseline: $^{**}P<0.01$, $^{***}P<0.001$

	Isoflurane (n=38)	Halothane (n=37)
Baseline	1.8 (1.4–2.2)	2.1 (1.6–2.9)
1 h after induction	1.9 (1.4–2.3)	2.3 (1.7–3.0)
2 h after induction	3.2 (2.4–4.4)***	3.9 (2.5–5.9)**
End of anaesthesia	3.3 (2.5–4.5)***	4.6 (2.9–7.2)***
1 h after anaesthesia	3.6 (2.8–4.7)***	5.2 (3.3–8.0)**
3 h after anaesthesia	2.6 (2.1–3.3)***	4.1 (2.8–6.0)***
6 h after anaesthesia	1.3 (1.0–1.6)**	1.8 (1.3–2.4)
24 h after anaesthesia	1.0 (0.7–1.4)***	1.7 (1.2–2.3)
Peak (µg litre^{-1})	4.3 (3.3–5.7)***	6.2 (4.1–9.5)***
AUC (µg litre^{-1} h)	6.9 (4.7–10.1)	7.0 (3.5–13.8)

Table 4 Aminotransferase activities (iu litre^{-1}) in serum (geometric mean (95% confidence interval). $^{**}P<0.01$ compared with baseline

	Isoflurane (n=38)	Halothane (n=37)
ALT baseline	14.9 (13.0–17.5)	17.4 (15.0–20.3)
24 h after anaesthesia	12.6 (11.0–14.6)**	15.2 (12.0–19.1)
AST baseline	18.1 (16.2–20.2)	20.0 (18.3–22.0)
24 h after anaesthesia	17.7 (15.8–19.9)	17.7 (15.5–20.3)**

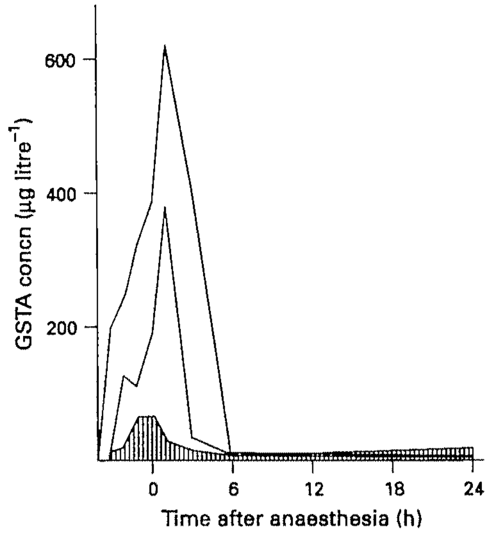

Figure 1 GSTA concentrations in serum. Lines indicate GSTA concentrations in two patients who exhibited an unexpectedly large increase in GSTA after halothane anaesthesia. Hatched area contains all GSTA concentrations in the other 73 patients, including a secondary increase in one patient 24 h after isoflurane anaesthesia.

groups, but heart rate was higher in the isoflurane group (table 2).

Seven patients in the isoflurane group and eight patients in the halothane group were hypotensive during anaesthesia. AUC values of hypotension ranged from 110 to 790 mm Hg min (median 290 mm Hg min) in the isoflurane group and from 100 to 450 mm Hg min (median 220 mm Hg min) in the halothane group.

GSTA concentrations varied in the isoflurane and halothane groups at successive times ($P<0.001$, repeated measures ANOVA). GSTA concentrations were significantly ($P<0.01$) higher than baseline from 2 h after induction to 3 h after the end of anaesthesia in both groups. In the isoflurane group, GSTA concentration was less than baseline at 6 and 24 h after the end of anaesthesia ($P<0.01$) (table 3). There were no significant differences in GSTA concentrations between the isoflurane and halothane groups during the study. Neither the peak nor AUC of GSTA differed significantly between the isoflurane and halothane groups (table 3). There were nine patients in the isoflurane group and 12 patients in the halothane group with peak GSTA values above the reference range during or immediately after anaesthesia. One patient exhibited an unexplained secondary increase in GSTA from 1.4 to 19.1 µg litre^{-1} at 24 h after isoflurane anaesthesia.

The peak concentration of GSTA (geometric mean) was 4.7 (95% confidence interval 3.4–6.6) µg litre^{-1} in hypotensive patients and 5.3 (3.9–7.2) µg litre^{-1} in normotensive patients (ns). The corresponding results for AUC were 5.3 (2.4–11.8) µg litre^{-1} h and 7.4 (4.8–11.5) µg litre^{-1} h (ns), respectively. The increase in GSTA was not associated with the addition of nitrous oxide, duration of anaesthesia (<180 min *vs* ≥180 min), type of surgery, malignancy, peroperative bleeding (<500 ml *vs* ≥500 ml), age (<40 yr *vs* ≥40 yr), sex or BMI (<23 kg m^{-2} *vs* ≥23 kg m^{-2}) when the peak and AUC values of GSTA were compared by *t* test and the successive GSTA concentrations with repeated measures ANOVA with one grouping factor (each of those mentioned above) or two grouping factors (volatile anaesthetic and each of those mentioned above).

Two patients (aged 46 and 53 yr; BMI 27.0 and 27.3 kg m^{-2}) exhibited an unexpectedly large increase in GSTA during and after halothane anaesthesia for surgery of breast cancer (fig. 1). There was a rapid decrease in GSTA to the reference range after anaesthesia in these two patients. No other signs or symptoms except for an increase in ALT (from 25 to 50 iu litre^{-1} and from 17 to 121 iu litre^{-1}) were observed and no obvious reason for the increase in GSTA was evident. Both patients recovered normally and ALT, AST, glutamyl transferase, bilirubin and GSTA concentrations were within reference ranges in control samples approximately 1 yr later.

There was a minor decrease in aminotransferase activities (table 4), but no significant difference between groups. There were no clinical signs or symptoms of hepatic disorder in any patient.

Discussion

We found a small, short-lasting increase in GSTA concentrations in serum after isoflurane and halothane anaesthesia. This indicated a mild subclinical disturbance in hepatocellular integrity.[1] The mechanisms of the hepatic effect are unclear. Hypotension, nitrous oxide, duration of anaesthesia, type of surgery, malignancy, bleeding, age, sex or BMI were not associated with the increase in GSTA. An unexplained secondary increase in GSTA without significant primary peak in the isoflurane group was similar to that described in previous studies.[1 2 4]

The lack of difference in GSTA between isoflurane and halothane contrasts with the results of earlier studies.[1 2] Compared with the study of

Murray, Rowlands and Trinick,[2] we exposed younger patients (mean age 41 *vs* 59 yr) to lower concentrations of inhalation anaesthetics (1.0 *vs* 2.0 MAC) for shorter intervals (mean duration 3.2 *vs* 10 h). In their study,[2] aspartate aminotransferase activity increased to 110 iu litre^{-1} (mean) 48 h after anaesthesia, which suggests more advanced disturbance in hepatocellular integrity than in studies without any increase in aminotransferases.[1 3] The relatively insensitive enzyme immunoassay for GSTA used by Murray, Rowlands and Trinick,[2] and infrequent sampling after anaesthesia may be the reason why there was no change in GSTA concentration after isoflurane anaesthesia.

The discrepancy between our study and that of Hussey and colleagues[1] is unclear. Patients with recent exposure to halothane (within 6 months) were not included in either study but differences in earlier exposure to halothane could be a confounding factor. We speculate that differences in the concentrations of inhalation anaesthetics and ventilation mode may explain why Hussey and colleagues[1] obtained higher GSTA concentrations after halothane than after isoflurane anaesthesia. The concentration of volatile anaesthetic was standardized (about 1.0 MAC) in our study. Ventilation was controlled mechanically and normoventilation was achieved by monitoring end-tidal $P\text{CO}_2$. In contrast, in the study of Hussey and colleagues,[1] the inspiratory concentration of volatile anaesthetic varied (1.0–3.0% isoflurane and 1.0–1.5% halothane in oxygen–nitrous oxide) and ventilation was spontaneous.

There is substantial evidence that immunological mechanisms may cause delayed hepatic injury after halothane anaesthesia (halothane hepatitis).[12] However, the time course of the changes in GSTA in our study did not indicate immunological mechanisms. Very deep anaesthesia is deleterious to the hepatic circulation.[13] This effect is more pronounced with halothane than with other anaesthetics, but the differences are small at 1 MAC concentration.[13] The direct toxicity of halothane on hepatocytes under hypoxic conditions or glutathione depletion could also cause liver injury, but in a recent well-controlled study[14] the authors rejected these mechanisms.

It would be tempting to implicate halothane as the cause of the unexpectedly large increase in GSTA in two of our patients after halothane anaesthesia. However, we found no mechanism to explain the relatively large changes in GSTA. Neither of these patients used any medication nor had any other known disease except breast cancer. They were not hypotensive during anaesthesia. Both had been anaesthetized twice, 1–22 yr before the present anaesthetic. A volatile anaesthetic (isoflurane) had been administered in one of the previous anaesthetics.

By using a sensitive immunoassay for measurement of serum concentrations of GSTA, we have previously detected small increases in GSTA after halothane,[3] sevoflurane[3] and propofol[4] anaesthesia. This study showed that hepatocellular integrity appeared to be disturbed to a similar degree during general anaesthesia with isoflurane or halothane at 1.0 MAC concentration. However, in two patients halothane anaesthesia was associated with large increases in serum concentrations of GSTA with minor increases in ALT. The significance of this is not clear.

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References

1. Hussey AJ, Aldridge LM, Paul D, Ray DC, Beckett GJ, Allan LG. Plasma glutathione S-transferase concentration as a measure of hepatocellular integrity following a single general anaesthetic with halothane, enflurane or isoflurane. *British Journal of Anaesthesia* 1988; **60**: 130–135.
2. Murray JM, Rowlands BJ, Trinick TR. Indocyanine green clearance and hepatic function during and after prolonged anaesthesia: comparison of halothane with isoflurane. *British Journal of Anaesthesia* 1992; **68**: 168–171.
3. Taivainen T, Tiainen P, Meretoja OA, Räiha L, Rosenberg PH. Comparison of sevoflurane and halothane on the quality of anaesthesia, serum glutathione transferase alpha and fluoride in paediatric patients. *British Journal of Anaesthesia* 1994; 73: 590–595.
4. Tiainen P, Lindgren L, Rosenberg PH. Disturbance of hepatocellular integrity associated with propofol anaesthesia in surgical patients. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 840–844.
5. Darling JR, McBride DR, Trinick TR, Murray JM, Fee JPH. Comparison of the effects of sevoflurane with those of isoflurane on hepatic glutathione-S-transferase concentration after body surface surgery. *British Journal of Anaesthesia* 1994; **73**: 268P.
6. Murray JM, Phillips AS, Fee JPH. Comparison of the effects of isoflurane and propofol on hepatic glutathione-S-transferase concentrations during and after prolonged anaesthesia. *British Journal of Anaesthesia* 1994; **72**: 599–601.
7. Tiainen P, Puustinen A, Rosenberg PH, Karhi KK. Enzyme immunoassay and time-resolved immunofluorometric assay for glutathione transferase Alpha compared. *Clinical Chemistry* 1996; **42**: 334–335.
8. Tiainen P, Höckerstedt K, Rosenberg PH. Hepatocellular integrity in liver donors and recipients indicated by glutathione transferase Alpha. *Transplantation* 1996; **61**: 904–908.
9. Tiainen P, Karhi KK. Ultrasensitive time-resolved immunofluorometric assay of glutathione transferase Alpha in serum. *Clinical Chemistry* 1994; **40**: 184–189.
10. Wilkinson L. *Systat: the System for Statistics.* Evanston, IL: Systat Inc., 1987.
11. Machin D, Cambell MJ. Comparing two means. In: *Statistical Tables for the Design of Clinical Trials.* Oxford: Blackwell Scientific Publications, 1987; 79–88.
12. Gut J, Christen U, Frey N, Koch V, Stoffler D. Molecular mimicry in halothane hepatitis: biochemical and structural characterization of lipoylated autoantigens. *Toxicology* 1995; **97**: 199–224.
13. Frink EJ, Morgan SE, Coetzee A, Conzen PF, Brown BR jr. The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs. *Anesthesiology* 1992; **76**: 85–90.
14. Johnson ME, Sill JC, Uhl CB, Van Dyke RA. Effect of halothane on hypoxic toxicity and glutathione status in cultured rat hepatocytes. *Anesthesiology* 1993; **79**: 1061–1074.

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Standardization of non-invasive impedance cardiography for assessment of stroke volume: comparison with thermodilution

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Summary

Since its introduction by Kubicek and colleagues, impedance cardiography has been suggested as a non-invasive, simple, safe and cost-effective method of measuring stroke volume. Several controversial reports on its validity have been published. Pitfalls of this method included the nature of the electrode system and the validity of the equations. Therefore, the purpose of this study was to compare two different spot electrode arrays and the two most frequently used stroke volume equations with each other and with thermodilution. In 37 patients, 24–36 h after cardiac surgery, we performed simultaneous measurements of stroke volume with impedance cardiography (SV_{IC}) and with thermodilution (SV_{TD}). SV_{IC} was obtained using the lateral spot (LS) electrode array, according to Bernstein, and a newly proposed modified semi-circular (MSC) spot electrode array. The equations of Kubicek and Sramek–Bernstein were used to calculate SV_{IC}. The Sramek–Bernstein equation was valid only when the LS array was used; the Kubicek equation determined SV_{TD} correctly only when the MSC array was used. However, a considerably better correlation and agreement (mean difference (2 SD)) was found between SV_{IC} and SV_{TD} for the latter ($r = 0.90$, 0.5 (17.1) ml *vs* $r = 0.64$, −4.9 (31.8) ml for the Sramek–Bernstein equation). We conclude that the most valid measurement of stroke volume using impedance cardiography was obtained when the MSC array was used together with Kubicek's equation. (*Br. J. Anaesth.* 1996; **77**: 748–752)

Key words
Measurement techniques, impedance cardiograpy. Measurement techniques, thermodilution. Monitoring, stroke volume. Model, mathematical.

The technique of impedance cardiography (IC) has gained popularity as a low-cost, simple, safe and non-invasive method of monitoring cardiac function. As a measure of cardiac systolic time intervals, its validity has received strong support.[1 2] However, as a method of monitoring stroke volume (SV), for which it has attracted the most interest, IC remains a controversial method.[3–6] One of the pitfalls of this method may be the substantial degree of methodological diversity that exists in the use of IC.

Impedance cardiography was introduced into clinical practice by Kubicek and colleagues[7 8] using their proposed equation and band electrode array. However, the band electrodes are not practical for use; they are difficult to apply correctly and uncomfortable for the patient, particularly in the intensive care unit.[5] New electrode arrays were introduced using disposable spot electrodes. The spot electrode array most frequently used now is the eight spot electrode array according to Bernstein.[9] Bernstein also introduced a new equation, based on the findings of Sramek, Rose and Miyamoto[10] to calculate stroke volume from the impedance cardiogram at the same time. This resulted in several studies comparing the Kubicek and Sramek–Bernstein equations.[11 12] However, apart from incidental notes, no reports have been published in which replacement of the band electrodes by the eight spot electrodes has been evaluated. Therefore, we compared recently the band electrode array according to Kubicek and colleagues and the eight spot electrode array according to Bernstein.[9] From this study we concluded that with the latter, significantly different information was obtained. Furthermore, it was shown, in an additional study,[14] that the eight spot electrode array generated a less homogeneous electrical field, which is one of the essentials for IC. In addition, a new spot electrode array was proposed which generates a far better homogeneous electrical field and produces the same information as the original band electrode array. These studies were performed in healthy subjects.

In this study we evaluated measurement of SV with IC, using the newly proposed spot electrode array, after coronary bypass surgery. This array was compared with the standard Bernstein array and combined with both the Kubicek and the Sramek–Bernstein equations.

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Patients and methods

We studied 40 patients, all 70 yr or less, undergoing coronary bypass surgery. The number of coronary bypasses during surgery varied from 1 to 6. Patients were excluded if they were haemodynamically unstable, showed cardiac arrhythmias or if there were variations in the separate thermodilution cardiac output measurements of more than 15% of the mean.

The study was approved by the institutional Human Ethics Committee and all patients gave informed consent.

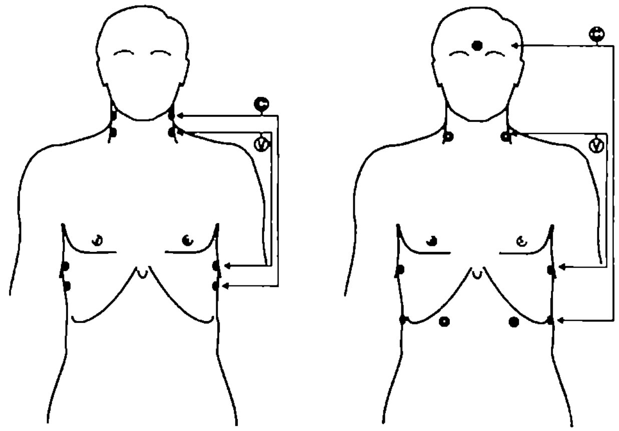
IMPEDANCE CARDIOGRAPHY

All impedance measurements were performed with the IPG-104 impedance Mini-Lab (RJL, Systems, Detroit, USA and Sanofi Sante, Maassluis, The Netherlands). The impedance cardiogram (d*Z*) and its first derivative (d*Z*/d*t*) were recorded in each patient using two different electrode configurations: an eight spot electrode configuration and a nine spot electrode configuration (fig. 1). The eight spot electrode configuration, as proposed originally by Bernstein,[9] uses four voltage detecting electrodes: two on each lateral site in the base of the neck and two on each lateral site of the thorax. Another four current ejecting electrodes are applied: two 5 cm above and two 5 cm below the voltage detecting electrodes in the neck and on the thorax, respectively. According to Sramek, Rose and Miyamots[10] the recommended distance between the voltage measuring electrodes is 17% of a person's height. In order to standardize the distance between the voltage detecting electrodes and exclude any anatomical abnormalities of the xiphisternum, this percentage was calculated and used as distance in order to place the caudal voltage electrodes on the thorax.

The nine spot electrode configuration (modified semi-circular (MSC) array) uses the same voltage detecting electrodes as the eight spot configuration. However, five current injecting electrodes are applied: one placed on the forehead of the patient and four in a semi-circular manner low on the abdomen: two in the mid-axillary lines and two in the mid-clavicular lines, all 15 cm caudal from the voltage detecting electrodes on the thorax. This array was developed recently in our laboratory. Measurements using the MSC array were comparable with those performed with the original band electrode array in a former study by our group.[14]

In each array, electrodes in one horizontal level were connected electrically and a sinusoidal current at 0.8 mA RMS and 60 kHz was passed between the cranial and caudal current injecting electrodes, and the resulting voltage was measured between the inner pairs. As current strength was known, impedance could be calculated.

Simultaneously with the impedance recordings, lead I of the ECG was recorded. All data from the impedance cardiograph and the ECG were stored digitally and averaged using our data acquisition system. From the averaged signal, left ventricular ejection time (LVET) was determined manually, as described by Lababidi and colleagues[15] and maximum impedance change (d*Z*/d*t*max) was measured from baseline (zero).



Lateral spot electrode array

Modified semi-circular electrode array

Figure 1 Spot electrode configurations, as used in this study, where C = current injecting electrodes and V = voltage measuring electrodes. The spot electrodes at one horizontal level are always electrically connected.

CALCULATIONS

For calculation of SV from the impedance cardiogram (SV_{IC}), impedance signals of 20 heart beats were averaged according to Kim, Song and Lee[16] in order to eliminate the effect of respiration.[17] In this way highly reproducible data can be obtained.[18]

SV_{IC} was calculated according to the equation of Kubicek and colleagues,[7 8]

$$SV = \rho \times (l^2/Z_0^2) \times dZ/dt\text{max} \times LVET$$

where SV = stroke volume (ml), ρ = resistivity of blood (Ω cm) calculated from the packed cell volume (PCV) according to Geddes and Sadler[19] and Hill and Thompson[20], l (cm) = inner distance between the voltage detecting electrodes (as calculated previously as 0.17 times a person's height), Z_0 = baseline thoracic impedance (Ω) read directly from a digital display on the impedance cardiograph, d*Z*/d*t*max = maximum rate of change of impedance during systole ($\Omega\ s^{-1}$) and LVET = left ventricular ejection time (s).

In addition to the equation of Kubicek and colleagues, the Sramek–Bernstein equation was also used to calculate SV_{IC}[9 10]

$$SV = \sigma \times (l^3/4.25)/Z_0 \times dZ/dt\text{max} \times LVET$$

where σ = a dimensionless weight correction factor according to Bernstein.[9] Both calculations were performed for each electrode configuration for each patient.

/

THERMODILUTION

A pulmonary artery catheter (Baxter/Edwards, Irvine, USA) was inserted in the perioperative period via the right internal jugular vein. Saline 0.9% (10 ml) with a temperature of 5 °C was injected manually with a closed injection system. The moment of injection of saline was chosen randomly. Stroke volume (SV_{TD}) was calculated automatically using a stroke volume computer (Marquette electronics Inc., Milwaukee, WI, USA). This procedure was repeated four times; the average of these four measurements was taken as SV_{TD}. All separate SV_{TD} measurements had to be within 15% of their mean, otherwise measurements were rejected and the patient was withdrawn from the study.

All measurements were performed 24–36 h after the coronary bypass operation. At the time of measurements all patients were breathing spontaneously. The sequence of the electrode configurations was chosen randomly.

STATISTICAL ANALYSIS

Linear regression analysis was performed to describe the relation between SV_{IC}, as calculated by each of the equations, and SV_{TD} for each electrode configuration. The paired Student's *t* test was used to compare data from both arrays. The level of statistical significance was set at $P < 0.05$. Bias plots according to the principles detailed by Bland and Altman[21] were also drawn.

Data were analysed for the whole group and separately for the two sexes.

Results

After exclusion of three patients because of large variations in the four SV_{TD} values obtained, SV measurements of 37 patients were evaluated; 28 men (mean weight 81.0 (SD 9.9) kg, *l* 30.0 (1.3) cm, PCV 30.5 (2.7) %, age 59.9 (range 41–72) yr) and nine women (weight 71.0 (9.4) kg, *l* 28.1 (0.8) cm, PCV 28.8 (2.9) %, age 63.3 (45–78) yr).

There were no significant differences in LVET between measurements from both electrode arrays. Using the LS array, we found a significantly higher Z_0 compared with the MSC array in both men and women (table 1). Only in men was dZ/d$t$max significantly lower with the LS array.

SV_{IC} did not differ significantly from SV_{TD} when the LS array was used together with the Sramek–Bernstein equation or when the MSC array was used in combination with the Kubicek equation to calculate SV_{IC} (table 2). Other combinations of electrode arrays and equations always led to a significant difference between the two methods. These findings were similar for both men and women.

Table 1 Comparison of impedance cardiographic variables obtained with the two different electrode configurations. (mean (SD)). *Significantly different from the same variable with the LS array ($P<0.05$)

Variable	Sex	LS array	MSC array
Z_0 (Ω)	M	24.3 (3.2)	18.0 (2.4)*
Z_0 (Ω)	F	30.2 (3.3)	22.1 (2.1)*
Z_0 (Ω)	M+F	25.6 (4.1)	18.9 (2.9)*
dZ/d$t$max (Ω s^{-1})	M	0.71 (0.3)	0.73 (0.3)*
dZ/d$t$max (Ω s^{-1})	F	0.95 (0.3)	0.95 (0.3)
dZ/d$t$max (Ω s^{-1})	M+F	0.77 (0.3)	0.78 (0.3)
LVET (s)	M	0.33 (0.04)	0.33 (0.04)
LVET (s)	F	0.31 (0.03)	0.31 (0.03)
LVET (s)	M+F	0.33 (0.04)	0.33 (0.04)

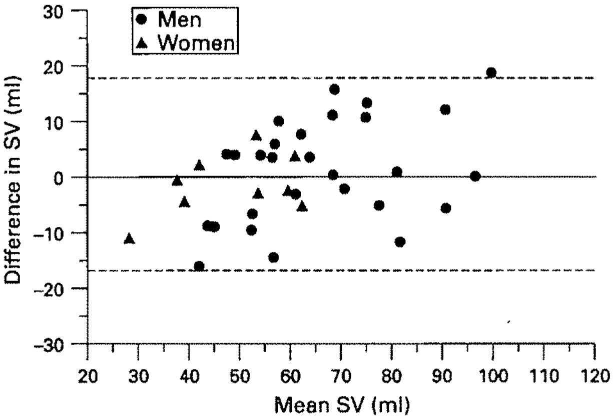


Figure 2 Difference between measurements of stroke volume (SV), as determined using thermodilution and Kubicek's method of impedance cardiography together with the MSC electrode array, *vs* mean of the two values; mean difference (—) and 95% confidence limits (—) are shown.

The highest correlation coefficients and the best agreement between the two methods in the whole group were found when the MSC array was used together with the Kubicek equation (table 2). In figure 2 the bias plot is shown for the relation between SV_{IC} and SV_{TD} using Kubicek's method of

Table 2 Comparison and correlation coefficients between SV_{IC} and SV_{TD} values (mean (SD)). K = Kubicek; SB = Sramek–Bernstein; SV_{TD} = stroke volume determined by thermodilution; SV_{IC} = stroke volume determined by impedance cardiography; MD (2 SD) = mean difference (2 SD) between SV_{IC} and SV_{TD}, *i*, *s* and *r* intercept, slope and correlation coefficient, respectively, for the correlation between SV_{IC} and SV_{TD}. *Significantly different from SV_{TD} ($P<0.05$)

Equation	Sex	SV_{TD} (ml)	SV_{IC} (ml)	MD (2 SD)	*i*	*s*	*r*
Lateral spot electrode array							
K	M	65.2 (14.9)	37.4 (12.1)*	−29.1 (25.1)	4.1	0.5	0.59
K	F	49.2 (11.2)	25.1 (7.8)*	−24.1 (13.8)	−2.2	0.6	0.79
K	M+F	61.3 (15.6)	34.5 (12.3)*	−27.9 (23.1)	0.2	0.5	0.69
SB	M	65.2 (14.9)	62.4 (18.9)	−4.9 (31.8)	10.9	0.8	0.59
SB	F	49.2 (14.9)	53.2 (15.7)	4.0 (14.8)	−9.1	1.3	0.90
SB	M+F	61.3 (15.6)	60.3 (18.5)	−2.7 (29.3)	12.4	0.8	0.64
Modified semi-circular spot electrode array							
K	M	65.2 (14.9)	67.1 (17.7)	0.9 (18.6)	−3.5	1.1	0.86
K	F	49.2 (11.2)	47.8 (13.4)	−1.4 (10.8)	−6.6	1.1	0.92
K	M+F	61.3 (15.6)	62.7 (18.6)	0.5 (17.1)	−5.0	1.1	0.90
SB	M	65.2 (14.9)	84.0 (23.8)*	17.2 (33.9)	4.0	1.2	0.73
SB	F	49.2 (11.2)	74.9 (23.0)*	25.7 (28.9)	−12.8	1.8	0.86
SB	M+F	61.3 (15.6)	81.9 (23.7)*	19.3 (33.2)	11.8	1.1	0.73

impedance cardiography together with the MSC electrode configuration.

Discussion

In this study we obtained impedance measurements with two electrode configurations: the LS array and the MSC array. SV_{IC} was calculated using the Kubicek and Sramek–Bernstein equations and all SV_{IC} values were compared with the respective SV_{TD} measurements. As mentioned previously it has been shown in a recent study by our group[14] that measurements obtained with the MSC array are comparable with those made with the original band electrode array.

Although d*Z*/d*t*max was significantly lower with the LS array in men, the main difference between the measurements from both arrays was in the determination of Z_0. This difference was the main cause of the varying results in the calculation of SV_{IC}. Independent of the equation, SV_{IC} was always significantly lower with the LS array than with the MSC array. The difference in Z_0 between measurements from both arrays cannot be considered as a trend between both arrays; independent of the equation used to calculate SV_{IC}, the correlation coefficients between SV_{IC} and SV_{TD} were considerably lower, in general, for the LS array. This finding may be explained by the fact that the LS array generates a less homogeneous electrical field,[14] indicating that Z_0 values between patients were not comparable. The MSC array, however, generates a far better homogeneous electrical field.[14]

The Kubicek equation showed considerably better correlation coefficients and a better agreement between SV_{IC} and SV_{TD} compared with the Sramek–Bernstein equation. It is remarkable how the Sramek–Bernstein equation appeared to be valid only when the LS array was used, and the Kubicek equation calculated SV_{TD} accurately only when the MSC array was used. In our opinion, this may be caused by the different use of Z_0 and l in both equations.

The best results were found when the Kubicek equation was used together with the MSC electrode array. However, despite the good correlation coefficient between SV_{IC} and SV_{TD} ($r = 0.90$), the Bland and Altman relation revealed that the difference in stroke volume between the two techniques could approach 17 ml. This indicates an error of up to 25% for an actual stroke volume of 70 ml. However, it is important to emphasize that this is also a result of the inaccuracy of the reference method used in this study (thermodilution[22]).

Data were analysed separately for both sexes. It is known that in women, higher Z_0 values are found together with a relative increase in d*Z*/d*t*max.[23 24] However, the effect of this difference between men and women on calculation of SV_{IC} has never been evaluated in comparison with thermodilution. Although only nine women were enrolled in this study, there was no evidence that SV_{IC} was calculated inaccurately in women.

We cannot comment on the validity of IC in the determination of stroke volume changes, as each point in figure 2 relates to a single individual. Further work is needed to determine the validity of the impedance cardiographic technique in the measurement of stroke volume changes in a single patient, for example when their condition deteriorates or improves. Monitoring of stroke volume together with its course may be a useful and important application of the impedance cardiographic technique in clinical anaesthesia.

We conclude that the LS array should not be used in impedance cardiography. We recommend the MSC array together with Kubicek's equation in the use of IC, because with this combination, optimal results may be expected. In order to standardize the method of IC we propose that this combination should be used together with the averaging sample technique, according to Kim, Song and Lee,[16] in order to eliminate the effect of respiration.

References

1. Balasubramanian V, Mathew OP, Behlal A, Tewari SC, Hoon RS. Electrical impedance cardiogram in derivation of systolic time intervals. *British Heart Journal* 1978; 40: 268–275.
2. Sheps DS, Petrovick ML, Kezakevich PN, Wolfe C, Craige E. Continuous noninvasive monitoring of left ventricular function during exercise by thoracic impedance cardiography—automated derivation of systolic time intervals. *American Heart Journal* 1982; 103: 519–524.
3. Goldstein DS, Cannon RO, Zimlichman R, Keiser HR. Clinical evaluation of impedance cardiography. *Clinical Physiology* 1986; 6: 235–251.
4. Denniston JC, Maher JT, Reeves JC. Measurement of cardiac output by electrical impedance at rest and during exercise. *Journal of Applied Physiology* 1976; 40: 91–95.
5. Donovan KD, Dobb GJ, Woods WP, Hockings BE. Comparison of transthoracic electrical impedance and thermodilution methods for measuring cardiac output. *Critical Care Medicine* 1986; 14: 1038–1044.
6. Bernstein DP. Continuous noninvasive real time monitoring of stroke volume and cardiac output by thoracic electrical bioimpedance. *Critical Care Medicine* 1986; 14: 898–901.
7. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. *Aerospace Medicine* 1966; 37: 1208–1212.
8. Kubicek WG, Patterson RP, Wisoe DA. Impedance cardiography as a noninvasive method of monitoring cardiac function and other parameters of the cardiovascular system. *Annals of the New York Academy of Sciences* 1970; 170: 724.
9. Bernstein DP. A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale. *Critical Care Medicine* 1986; 14: 904–909.
10. Sramek BB, Rose DM, Miyamoto A. Stroke volume equation with a linear base impedance model and its accuracy as compared to thermodilution and magnetic flowmeter techniques in humans and animals. *Proceedings of the Sixth International Conference on Electrical Bioimpedance*, Zadar, Yugoslavia, 1983; 38.
11. Gotshall RW, Wood VC, Miles DS. Comparison of two impedance cardiographic techniques for measuring cardiac output in critically ill patients. *Critcal Care Medicine* 1990; 17: 806–811.
12. DeMey C, Enterling D. Noninvasive assessment of cardiac output by impedance cardiography: Disagreement between two equations to estimate stroke volume. *Aviation Space and Environmental Medicine* 1988; 59: 57–62.
13. Woltjer HH, Van der Meer BJ, Bogaard HJ, de Vries PM. Comparison between spot and band electrodes and between two equations for calculation of stroke volume by means of impedance cardiography. *Medical and Biological Engineering and Computing* 1995; 33: 330–334.
14. Woltjer HH, Arntzen BWGJ, Bogaard HJ, de Vries PMJM. Optimalization of the spot electrode array in impedance

cardiography. *Medical and Biological Engineering and Computing* 1995; **34**: 1–4.

15. Lababidi Z, Ehmke DA, Durnin RE, Leaverton PE, Lauer RM. The first derivative thoracic impedance cardiogram. *Circulation* 1970; **41**: 651–658.
16. Kim DW, Song CG, Lee MH. A new ensemble averaging technique in impedance cardiography for estimation of stroke volume during treadmill exercise. *Frontiers of Medical and Biological Engineering* 1992; **4**: 179–188.
17. Verschoor N, Woltjer HH, van der Meer BJM, de Vries PMJM. The lowering of stroke volume measured by means of impedance cardiography during endexpiratory breath holding. *Physiological Measurements* 1996; **17**: 29–35.
18. De Souza WM, Panerai RB. Variability of thoracic impedance cardiograms in man. *Medical and Biological Engineering and Computing* 1981; **19**: 411–415.
19. Geddes LA, Sadler C. The specific resistance of blood at body temperature. *Medical and Biological Engineering and Computing* 1973; **11**: 336–339.
20. Hill DW, Thompson FD. The importance of blood resistivity in the measurement of cardiac output by the thoracic impedance method. *Medical and Biological Engineering and Computing* 1975; **3**: 187–190.
21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
22. Stetz CW, Miller RG, Kelly GE, Raffin TA. Reliability of the thermodilution method in the determination of cardiac output in clinical practise. *American Review of Respiratory Disease* 1982; **126**: 1001–1004.
23. Frey MABF, Doerr BM, Miles DS. Transthoracic impedance: differences between men and women with implications for impedance cardiography. *Aviation and Space Environmental Medicine* 1982; **53**: 1190–1192.
24. McKinney ME, Buell J, Eliot RS. Sex differences in transthoracic impedance: evaluation of effects on calculated stroke volume index. *Aviation and Space Environmental Medicine* 1984; **55**: 893–895.

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Lack of specific renal haemodynamic effects of different doses of dopamine after infrarenal aortic surgery

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Summary

Dopamine is administered frequently in the operating theatre and intensive care unit patients undergoing mechanical ventilation with the aim of specifically enhancing renal blood flow. In an uncontrolled, open study, we administered sequentially different doses of dopamine (0, 2, 4, 8 and 0 μg kg^{-1} min^{-1}) during a 1-h period each. Systemic haemodynamic and renal haemodynamic variables were measured simultaneously using a pulmonary artery catheter and radiopharmaceuticals, respectively. We studied seven haemodynamically stable patients (mean age 66 yr), with a serum creatinine concentration < 160 μmol $litre^{-1}$, after elective infrarenal abdominal aortic reconstruction. All patients received extradural analgesia with bupivacaine and sufentanil, and none had a previous history of heart failure. Dopamine induced a dose-dependent increase in cardiac index which returned to baseline after cessation of the dopamine infusion. Glomerular filtration rate (GFR) increased with all doses of dopamine, whereas renal blood flow (RBF) increased significantly only with the 2- and 4-μg kg^{-1} min^{-1} doses. However, the ratio RBF/cardiac output remained unchanged with the 2- and 4-μg kg^{-1} min^{-1} doses, but decreased with 8 μg kg^{-1} min^{-1} from 14 (1.5) % to 10 (1.3) %. We conclude that dopamine increased RBF and GFR as a result of an increase in cardiac output. (*Br. J. Anaesth.* 1996; **77**: 753–757)

Key words
Pharmacology, dopamine. Kidney, function. Kidney, blood flow. Surgery, vascular. Cardiovascular system, effects.

Dopamine, a naturally occurring catecholamine, has a complicated influence on the cardiovascular and renal systems. This is because dopamine stimulates different types of adrenergic receptors: not only α- and β-adrenergic but also specific dopamine receptors.[1] Dopamine can be used for various indications depending on the given dose. In doses of 0.5–3.0 μg kg^{-1} min^{-1}, the so-called "renal dose", the predominant effect of dopamine is a marked increase in renal plasma flow, glomerular filtration rate and sodium excretion. This is caused mainly by stimulation of dopamine receptors. In doses of 3–10 μg kg^{-1} min^{-1}, dopamine exerts positive inotropic effects, primarily as a result of β_1 receptor stimulation. In doses exceeding 10 μg kg^{-1} min^{-1}, dopamine induces vasoconstriction and positive chronotropism as a result of predominant α-adrenergic and β-adrenergic effects, respectively.

Alterations in renal blood flow may contribute to the initiation of events which lead to renal failure.[2] In the intensive care unit dopamine is often used in doses of up to 4 μg kg^{-1} min^{-1} to increase or preserve renal blood flow. In clinical practice dopamine is given during mechanical ventilation, particularly during positive end-expiratory pressure (PEEP) ventilation for this purpose. Cardiac output is decreased during PEEP,[3 4] leading to decreased renal blood flow. Furthermore, PEEP decreases the release of atrial natriuretic peptide.[5] The renal vasodilating and natriuretic properties of a low-dose infusion of dopamine are therefore believed to be beneficial.

In previous studies in healthy subjects and patients with congestive heart failure (CHF) we and others have demonstrated that renal blood flow and sodium excretion are increased by administration of dopamine or its analogues.[6–10] However, there are no clinical studies on the renal haemodynamic effects of different "low-dose" dopamine infusions during mechanical ventilation with PEEP and their relation to systemic haemodynamics. As cardiac output and venous return are altered significantly during mechanical ventilation, it is reasonable to argue that renal haemodynamics and the effects of low-dose dopamine may be different from results obtained in healthy volunteers and patients with CHF.

In our department patients are admitted after major vascular surgery where sedation and

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mechanical ventilation are continued until the patient is stable, and tracheal extubation is usually performed several hours after admission. Therefore, we performed a dose-finding study in these patients undergoing mechanical ventilation after operation to determine the dose of dopamine with the most pronounced renal haemodynamic effects.

Patients and methods

We studied seven consecutive postoperative patients admitted to the intensive care unit (ICU) who had undergone abdominal infrarenal aortic reconstruction, fulfilling the following inclusion criteria: stable haemodynamic state, defined as no need for inotropic drugs or rapid fluid administration and lack of active bleeding; normal hepatic function; stable ventilatory condition with a Pa_{O_2}/FI_{O_2} ratio > 25 kPa (FI_{O_2} = fractional inspiratory oxygen) with 8 cm of PEEP and normal airway pressures; and a preoperative serum creatinine concentration < 160 μmol litre^{-1}.

Patients receiving either α- or β-adrenergic agonists or antagonists, dopamine agonists or antagonists, monoamine oxidase inhibitors, angiotensin converting enzyme inhibitors or diuretics in the previous 3 months were excluded. Patients with a previous history of congestive heart failure were also excluded. All patients had a pulmonary artery catheter (Baxter Thermodilution Catheter, Edwards Laboratories, Irvine, CA, USA) inserted before operation for peroperative monitoring. The position was checked in the ICU by a standard chest roentgenogram. All patients had an extradural infusion of a combination of 0.125% bupivacaine and sufentanil 1 μg ml^{-1} at a rate of 8 ml h^{-1} for analgesia. Additional sedation comprised a continuous infusion of midazolam during the study. An infusion of 0.45%–2.5% sodium–glucose was given at a rate of 3500 ml day^{-1}. Potassium was administered according to serum potassium concentrations. Initially, supplements of crystalloids and colloids were given in the immediate postoperative phase and (mild) hypothermia was corrected. At the moment when no inotropic support and no additional rapid fluid infusion were required, the study was started. All patients gave written informed consent and the study was approved by the Medical Ethics Committee of the University Hospital of Groningen.

After haemodynamic stability was established and patients were normothermic, measurements were started after a further equilibration period of 1.5–2 h. After 1 h of baseline measurements, an infusion of dopamine was started. During the first hour the rate of infusion was 2 μg kg^{-1} min^{-1}. In the second and third hours this dose was increased to 4 and 8 μg kg^{-1} min^{-1}, respectively. During the fourth hour the dopamine infusion was decreased gradually over 10 min. At the end of this hour the study was terminated.

RENAL FUNCTION TESTS

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured simultaneously using ^{125}I-iothalamate and ^{131}I-hippurate, respectively, according to the method described by Donker and colleagues.[11] The radiopharmaceuticals were infused at a constant rate after a priming dose had been given. After the previously mentioned equilibration period of 1.5–2 h, clearances were determined every hour. Filtration fraction (FF) represents the ratio GFR/ERPF. Hourly urine samples were collected via a bladder catheter. Serum and urinary electrolyte concentrations were assayed by routine Technicon SMA-C Auto-Analyzer (Technicon, Tarrytown, NY, USA). After measurements of baseline values during the first hour, hourly measurements were performed during the subsequent 4 h.

HAEMODYNAMIC MEASUREMENTS

Using the pulmonary artery catheter, inserted via the jugular vein, cardiac output, pulmonary capillary wedge, pulmonary arterial and central venous pressures were measured every 30 min. Haemodynamic measurements and derived variables were determined as described previously.[12] Arterial pressure was measured via a radial arterial cannula. Haemodynamic data were measured together with renal function tests, thereby allowing simultaneous evaluation of the renal and systemic haemodynamic effects of dopamine.

PLASMA NEUROHUMORAL VARIABLES

Blood samples were obtained for measurement of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) at the end of each hour during the study. PRA and PAC were determined by radioimmunoassay. The intra-assay coefficients of variation were 5.2% and 8% for PRA and PAC, respectively. The inter-assay coefficient of variation was 15% for PAC and 10.3% for PRA. Serum catecholamine concentrations were determined by high pressure liquid chromatography (HPLC) with electrochemical detection, after an extraction procedure.[13]

STATISTICAL ANALYSIS

All data are given as mean (SEM), unless otherwise stated. Paired statistics were performed comparing baseline values with values at specific times, which means that every patient served as his own control. Paired t tests were used for normally distributed data, whereas the Wilcoxon test was used for non-normally distributed data. The software package SPSS for Windows, version 6.0 was used on a 486 DX personal computer. For non-normally distributed data, medians and ranges are given. All values for ERPF and GFR were corrected for a body surface of 1.73 m^2. Renal blood flow (RBF) was calculated as (uncorrected ERPF)/(1 − packed cell volume). The percentage renal blood flow–cardiac output (CO) ratio was calculated as RBF/CO × 100%. Differences were considered statistically significant at the 5% level.

Table 1 Renal and systemic haemodynamics. SVR=Systemic vascular resistance; GFR = glomerular filtration rate; RBF = renal blood flow. Systemic haemodynamics were determined every 30 min, whereas renal haemodynamics were determined every 60 min. The first value in each panel for a specific time indicates the value halfway between the hour for the systemic haemodynamics. *Significant difference compared with baseline; †significant difference compared with previous value

	Cardiac Index (litre min^{-1}m^{-2})	Heart rate (beat min^{-1})	SVR (dyn s cm^{-5})	GFR (ml min^{-1}/1.73 m^2)	RBF (ml min^{-1}/1.73 m^2)	RBF/CO ratio (%)
Baseline	2.77 (0.30)	84 (9.2)	1250 (131)			13.9 (1.6)
	2.77 (0.31)	84 (9.5)	1235 (133)	80 (8.8)	676 (116)	13.9 (1.5)
t1	2.97 (0.31)	82 (7.2)	1036 (134)			14.3 (1.9)
(Dopamine 2 μg kg^{-1}min^{-1})	2.90 (0.28)	84 (7.2)	1131 (167)	94 (12.6)*	737 (118)*	14.1 (1.3)
t2	3.34 (0.31)*	86 (7.2)	1067 (148)			13.8 (1.6)
(Dopamine 4 μg kg^{-1}min^{-1})	3.39 (0.22)*	88 (6.4)	984 (99)*	97 (13.2)*	809 (125)*	13.6 (1.6)
t3	4.24 (0.24)*	97 (6.3)*	944 (130)*			10.4 (1.3)*
(Dopamine 8 μg kg^{-1}min^{-1})	4.09 (0.23)*	102 (6.4)*	938 (112)*	101 (12.9)*	768 (107)	10.7 (1.3)*
t4	2.96 (0.32)*	87 (5.9)	1000 (135)			12.5 (0.9)
(Dopamine 0 μg kg^{-1}min^{-1})	2.93 (0.31)*	86 (5.9)	980 (120)	88 (9.9)*†	658 (105)	12.7 (1.1)

Results

We studied six males and one female, mean age 66 (range 46–77) yr. All underwent uncomplicated infrarenal abdominal aortic reconstruction.

EFFECTS ON SYSTEMIC AND RENAL HAEMODYNAMICS (TABLE 1)

A dose-dependent increase in cardiac index was observed, from 2.77 (0.30) litre min^{-1} m^{-2} at baseline to a maximum of 4.24 (0.24) litre min^{-1} m^{-2} with dopamine 8 μg kg^{-1} min^{-1}. After cessation of administration of dopamine, cardiac index returned to values comparable with baseline: 2.93 (0.31) litre min^{-1} m^{-2}. There were no significant increases in heart rate except with a dose of 8 μg kg^{-1} min^{-1}. Filling pressures (mean PACWP and CVP approximately 12 (1.2) and 8 (0.7) mm Hg, respectively), mean arterial pressure (approximately 90 (8) mm Hg) and pulmonary pressures (approximately 25 (2) mm Hg) remained unchanged during the study. Systemic and pulmonary vascular resistance decreased during infusion of the higher doses of dopamine and returned to values similar to baseline after dopamine was stopped.

Table 2 Effects of different doses of dopamine on renal function. *Significant difference compared with corresponding baseline values

	Urine volume (ml h^{-1})	Na$^+$ excretion (mmol h^{-1})	FeNa$^+$ (%)
Baseline	115 (24)	11.9 (3.7)	0.09 (0.03)
t1 (2 μg kg^{-1}min^{-1})	164 (50)	17.6 (7.4)*	0.12 (0.06)
t2 (4 μg kg^{-1}min^{-1})	260 (54)*	27.9 (8.0)*	0.2 (0.06)*
t3 (8 μg kg^{-1}min^{-1})	336 (56)*	36.0 (7.5)*	0.24 (0.05)*
t4 (0 μg kg^{-1}min^{-1})	140 (33)†	15.7 (4.8)	0.11 (0.03)

GFR increased for all doses of dopamine, from 80 (8.8) ml^{-1} min^{-1} per 1.73 m^2 to a maximum of 101 (12.9) ml^{-1} min^{-1} per 1.73 m^2. RBF increased from a mean of 676 (116) ml^{-1} min^{-1} per 1.73 m^2 to a maximum of 809 (125) ml^{-1} min^{-1} per 1.73 m^2 with the 4-μg kg^{-1} min^{-1} dose (table 1). Filtration fraction varied non-significantly during the study from 0.19 (0.01) to 0.21 (0.01). However, there was a decrease in the contribution of cardiac output to RBF with the 8-μg kg^{-1} min^{-1} dose (from 14 (1.5) % to 10 (1.3) %).

RENAL EFFECTS (TABLE 2)

Hourly urine volume increased from 115 (24) ml h^{-1} at baseline to 336 (56) ml h^{-1} with dopamine 8 μg kg^{-1} min^{-1}. Sodium concentration and fractional sodium excretion increased in a dose-dependent manner from 11.9 (3.7) mmol h^{-1} and 0.09 (0.03) % to 36.0 (7.5) mmol h^{-1} and 0.24 (0.05) %, respectively. All returned to values comparable with baseline at the end of the study when dopamine was stopped.

NEUROHORMONES AND CATECHOLAMINES (TABLE 3)

There were no significant changes in PRA during the study. Plasma concentrations of aldosterone were reduced significantly by dopamine 8 μg kg^{-1} min^{-1}. Median plasma concentrations of noradrenaline were increased significantly by dopamine infusion. After stopping dopamine, plasma concentrations of noradrenaline returned to values comparable with

Table 3 Neurohormones during the study period. Values are mean (SD) or median (range) for non-normally distributed data. Baseline 1 values were determined immediately before start of the study and baseline 2 values were determined at the end of the baseline period. *Significant difference compared with baseline values

	PRA (nmol litre^{-1}h^{-1})	Aldosterone (nmol litre^{-1})	Noradrenaline (nmol litre^{-1})	Adrenaline (nmol litre^{-1})
Baseline 1			3.08 (0.75–8.79)	0.82 (0.010–3.58)
Baseline 2	1.26 (0.31)	0.38 (0.11)	3.48 (0.25–10.0)	0.49 (0.010–2.35)
t1 (2 μg kg^{-1}min^{-1})	1.19 (0.31)	0.27 (0.07)	4.46 (0.74–14.2)*	0.20 (0.010–7.66)
t2 (4 μg kg^{-1}min^{-1})	1.09 (0.33)	0.19 (0.04)	9.96 (1.44–29.5)*	0.40 (0.10–9.55)
t3 (8 μg kg^{-1}min^{-1})	0.90 (0.28)	0.13 (0.02)*	19.66 (2.96–51.4)*	0.33 (0.05–8.57)
t4 (0 μg kg^{-1}min^{-1})	0.93 (0.24)	0.24 (0.06)	4.95 (1.07–33.1)	0.47 (0.010–1.96)

baseline. Dopamine concentrations increased from a median baseline value of 7.5 (range 2.0–11.3) nmol litre^{-1} to 413 (28.0–1840) nmol litre^{-1}. After stopping the infusion of dopamine, plasma concentrations of dopamine decreased to 11.9 (7.6–326) nmol litre^{-1}.

Discussion

We found that although dopamine increased GFR and RBF at different doses, no specific enhancement of renal flow was present. The increase in RBF was caused mainly by an increase in cardiac output. With dopamine 8 μg kg^{-1} min^{-1}, the fraction of cardiac output directed to the kidney was even decreased. Furthermore, dopamine acted as a diuretic in a dose-dependent manner, with an increase in diuresis and (fractional) sodium excretion. The decrease in plasma concentration of aldosterone, which may also have contributed to the natriuretic effect of dopamine, was related probably to dopamine DA_2 receptor stimulation of the adrenal zona glomerulosa.[14 15]

Dopamine is frequently administered in the ICU to patients undergoing mechanical ventilation to improve GFR and RBF. An improvement in mainly RBF has been shown in many studies investigating healthy volunteers or non-mechanically ventilated patients with congestive heart failure.[6 8 16–18] However, few data exist indicating an increase in renal perfusion in patients undergoing mechanical ventilation. Mostly, only estimates of renal function, such as creatinine clearance and diuresis are measured.[19 20] Additionally, in most studies the β-agonist activity of dopamine is insufficiently regarded, as cardiac output is not measured simultaneously.

Despite the frequently used terminology "renal dose" of dopamine, indicating a dose of dopamine with preferential effects on renal haemodynamics, our study showed that such a renal-selective dose did not exist. Furthermore, different doses of dopamine have been investigated in different studies. To our knowledge this is the first study examining different doses of dopamine in patients undergoing mechanical ventilation. However, all of our patients received thoracic extradural analgesia with bupivacaine and sufentanil. The resulting sympathetic block may interfere with the distribution of flow and therefore the RBF/CO ratio. Vascular DA_1 receptor stimulation results in predominant post-glomerular vasodilatation by direct vasodilatation of the efferent arterioles.[9 18] Because of this mechanism, a preferential increase in RBF has been observed in heart failure patients and in healthy subjects.[6–9 16] The results in our patients suggest that the renal vasodilating effects were outweighed by the systemic effects and were not caused by absent or decreased sympathetic innervation of the kidney, as in kidney transplant recipients a specific renal vasodilating effect of dopamine 2 μg kg^{-1} min^{-1} is still present (assuming the absence of sympathetic innervation in transplanted kidneys).[21] However, the filtration fraction in our patients was lower than that reported in healthy volunteers and (especially) heart failure patients,[8–10] which makes a further decrease in filtration fraction as an indication of specific renal vasodilatation more difficult to achieve.

If an increase in RBF and GFR is considered the goal of treatment, our data indicate that 4 μg kg^{-1} min^{-1} is the optimal dose of those studied. However, this is no reason to give dopamine and should not be considered as the "renal dose".

Dopamine increases stroke volume and cardiac output in a dose-dependent manner, with a maximal increase with the highest dose (8 μg kg^{-1} min^{-1}). Heart rate increased only with the highest dose of dopamine (8 μg kg^{-1} min^{-1}). The positive inotropic effect of dopamine is caused not only by its direct β_1-agonist activity, but also by inhibition of uptake-1.[22] Uptake-1 inhibition of dopamine may be involved in the increase in plasma concentrations of noradrenaline. Furthermore, as dopamine is a precursor of noradrenaline, stimulation of endogenous noradrenaline formation cannot be excluded. Additionally, dopamine may enhance release of noradrenaline via β_2-receptor stimulation. We found no effects on plasma renin activity or adrenaline. Although DA_1 receptor stimulation can increase PRA,[9] evidence exists that balanced DA_1 and DA_2 receptor stimulation does not alter PRA.[10] The most important stimulus for an increase in adrenaline concentration is hypoglycaemia and some evidence suggests that stimulation of adrenal DA_2 receptors, present on chromaffin cells, induces inhibition of adrenaline release.[23] This may explain why no increase in plasma concentrations of adrenaline was observed.

The reduction in systemic and pulmonary vascular resistance was an unexpected finding in our study. Several mechanisms may be involved; first, all patients received thoracic extradural analgesia, which causes sympathetic block. The influence of dopamine on ganglionic receptors is therefore modified. Second, DA_1 receptor-mediated effects, causing vasodilatation, may be involved and override direct α_1-receptor-mediated vasoconstrictive effects, even at this dose. Rajfer and colleagues[24] observed a decrease in vascular resistance with increasing plasma dopamine concentrations, with administration of levodopa, a dopamine prodrug. Lundberg and colleagues also observed a decrease in systemic vascular resistance during infusion of dopamine.[25]

Although our study was uncontrolled, recovery of all variables to (almost) baseline values after stopping dopamine infusion indicated a drug-related and not time-related effect. Our study further emphasizes the different effects of dopaminergic drugs in different categories of patients, as we and others have shown previously.[10 26 27]

Acknowledgement

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References

1. Goldberg LI. Cardiovascular and renal actions of dopamine; potential clinical applications. *Pharmacological Reviews* 1972; 24: 1–24.
2. Brenner M, Schaer GL, Mallory DL, Suffredini F, Parrillo JE. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. *Chest* 1990; 98: 170–179.

3. Jardin F, Farcot JC, Boisante L, Curien N, Magairaz A, Bourdarias JP. Influence of positive end-expiratory pressure on left ventricular performance. *New England Journal of Medicine* 1981; **304**: 387–392.
4. Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Huygebaert MF. Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. *Chest* 1986; **90**: 74–80.
5. Leithner C, Frass M, Pacher R. Mechanical ventilation with positive end-expiratory pressure decreases release of alpha-atrial natriuretic peptide. *Critical Care Medicine* 1987; **15**: 484–488.
6. Rosenblum R, Tai AR, Lawson D. Cardiac and renal hemodynamic effects of dopamine in man. *Clinical Research* 1970; **18**: 326
7. Goldberg LI. The role of dopamine receptors in the treatment of congestive heart failure. *Journal of Cardiovascular Pharmacology* 1989; **14** (Suppl. 5): S19–S27.
8. Smit AJ, Meijer S, Wesseling H, Donker AJM, Reitsma WD. Dissociation of renal vasodilator and natriuretic effects of dopamine during sulpiride infusion in normal man. *European Journal of Clinical Pharmacology* 1990; **39**: 221–226.
9. Girbes ARJ, Smit AJ, Meijer S, Reitsma WD. Renal and endocrine effects of fenoldopam and metoclopramide in normal man. *Nephron* 1990; **56**: 179–185.
10. Girbes AR, Kalisvaart CJ, Van Veldhuisen DJ, Tan ET, Smit AJ, Reitsma WD, Pasteuning WH. Effects of ibopamine on renal haemodynamics in patients with severe congestive heart failure. *European Heart Journal* 1993; **14**: 279–283.
11. Donker AJM, Hem van der GK, Sluiter WJ, Beekhuis H. A radioisotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. *Netherlands Journal of Medicine* 1977; **20**: 97–103.
12. Van Veldhuisen DJ, Girbes ARJ, Crijns H, Smit AJ, De Graeff PA, Lie KI. Efficacy and safety of ibopamine in congestive heart failure. *Journal of Autonomic Pharmacology* 1990; **10**: S115–S121.
13. Smedes F, Kraak JC, Poppe H. Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline and dopamine from plasma and urine. *Journal of Chromatography* 1982; **231**: 25–39.
14. Noth RH, McCallum RW, Contino C, Havelick J. Tonic dopaminergic suppression of plasma aldosterone. *Journal of Clinical Endocrinology and Metabolism* 1980; **51**: 64–69.
15. Missale C, Memo M, Liberini P, Spano P. Dopamine selectively inhibits angiotensin II-induced aldosterone secretion by interacting with D-2 receptors. *Journal of Pharmacology and Experimental Therapeutics* 1988; **246**: 1137–1143.
16. Ramdohr B, Schüren KP, Biamino G, Schröder R. Der Einfluss von Dopamine auf Haemodynamik und Nierenfunktion bei der schweren Herzinsuffizienz des Menschen. *Klinische Wochenschrift* 1973; **51**: 549–556.
17. Hansell P, Michaelsson K, Ulfendahl HR. Renal effects of atriopeptin II and dopamine receptor blockade in acutely volume-expanded rats. *Acta Physiologica Scandinavica* 1988; **133**: 35–40.
18. Wee PMt, Smit AJ, Rosman JB, Sluiter WJ, Donker AJM. Effect of intravenous infusion of low-dose dopamine on renal function in normal individuals and in patients with renal disease. *American Journal of Nephrology* 1986; **6**: 42–46.
19. Hemmer M, Suter PM. Treatment of cardiac and renal effects of PEEP with dopamine in patients with acute respiratory failure. *Anesthesiology* 1979; **50**: 399–403.
20. Duke GJ, Briedis JH, Weaver RA. Renal support in critically ill patients: low-dose dopamine or low-dose dobutamine? *Critical Care Medicine* 1994; **22**: 1919–1925.
21. ter Wee PM, Tegzess AM, Donker AJM. Pair-tested filtration capacity in kidney recipients and their donors. *Journal of the American Society of Nephrology* 1994; **4**: 1798–1808.
22. Deighton NM, Motomura S, Bals S, Zerkowski HR, Brodde OE. Characterization of the beta adrenoceptor subtype(s) mediating the positive inotropic effects of epinephrine, dopamine, dobutamine, denopamine and xamoterol in isolated human right atrium. *Journal of Pharmacology and Experimental Therapeutics* 1992; **262**: 532–538.
23. Mannelli M, Pupilli C, Lanzillotti R, Ianni L, Bellini F, Sergio M. Role for endogenous dopamine in modulating sympathetic–adrenal activity in humans. *Hypertension Research* 1995; **18**: S79–S86.
24. Rajfer SI, Rossen JD, Nemanich JW, Douglas FL, Davis F, Osinski J. Sustained hemodynamic improvement during long-term therapy with levodopa in heart failure: role of plasma catecholamines. *Journal of the American College of Cardiology* 1987; **10**: 1286–1293.
25. Lundberg J, Norgren L, Thomson D, Werner O. Hemodynamic effects of dopamine during thoracic epidural analgesia in man. *Anesthesiology* 1987; **66**: 641–647.
26. Fijter CWHd, Comans EFI, Vries PMJMd, et al. The effect of fenoldopam on renal haemodynamics and natriuresis in chronic renal failure. *Netherlands Journal of Medicine* 1990; **36**: 267–278.
27. Girbes ARJ, Van Veldhuisen DJ, Smit AJ, Drent-Bremer A, Meijer S, Reitsma WD. Renal and neurohumoral effects of ibopamine and metoclopramide in normal man. *British Journal of Clinical Pharmacology* 1991; **31**: 701–704.

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LABORATORY INVESTIGATIONS

Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors

C. S. GOODCHILD, Z. GUO, A. MUSGREAVE AND J. P. GENT

Summary

Intrathecal midazolam causes antinociception by combining with spinal cord benzodiazepine receptors. This effect is reversible with doses of naloxone, suggesting involvement of spinal κ or δ but not μ opioid receptors. The antinociceptive effects of intrathecally administered drugs in the spinal cord were demonstrated by measurements of the electrical current threshold for avoidance behaviour in rats with chronically implanted lumbar intrathecal catheters. A comparison was made of suppression by two opioid selective antagonists (nor-binaltorphimine (κ selective) and naltrindole (δ selective)) of spinal antinociception caused by equipotent doses of opioids selective for different receptor subtypes (U-50488H (κ), DSLET and DSBULET (δ), fentanyl (μ)) and the benzodiazepine midazolam. Nor-binaltorphimine selectively suppressed the effects of U-50488H but not midazolam or fentanyl. However, the δ selective antagonist, naltrindole, caused dose-related suppression of antinociception produced by both δ opioid agonists and midazolam with the same ED$_{50}$ (0.5 nmol). We conclude that intrathecal midazolam caused spinally mediated antinociception in rats by a mechanism involving δ opioid receptor activation. (*Br. J. Anaesth.* 1996; **77**: 758–763)

Key words
Pain, experimental. Analgesic techniques, regional, intrathecal. Analgesics opioid. Receptors, opioid. Hypnotics benzodiazepines, midazolam. Rat.

Intrathecal injection of midazolam has been shown to produce analgesia in humans[1,2] and antinociceptive effects in rats.[3,4] This effect in rats is caused by an action on GABA$_A$ receptors in the spinal cord and may also be produced by the archetypal benzodiazepine, chlordiazepoxide.[5–7] It has also been shown that the antinociceptive effects of intrathecal midazolam may be suppressed by the opioid antagonist naloxone and this effect was dose-dependent.[5,8] Doses that blocked the midazolam effects were similar to those needed to suppress the effects of the κ opioid agonist ketocyclazocine and significantly greater than those needed to block the effects of the μ selective opioid agonist, fentanyl.[5,8] The results from those experiments implied that intrathecal midazolam, after combining with GABA$_A$ receptors, caused the release of endogenous opioids that acted at a κ or δ but not a μ opioid receptor.

The aim of this study was to investigate the possible role of both of these opioid receptors in the production of spinally mediated antinociception by midazolam. This was achieved by observing the effects on spinal antinociception of different receptor-selective antagonists.

Materials and methods

These experiments were carried out with the permission of the Licensing Authorities of Great Britain under Home Office Licence No. PPL/50/001310 and in all cases the authors adhered to the Guidelines for Investigation of Pain in Experimental Animals.[9]

INTRATHECAL CANNULATION

Rats (150–200 g) were anaesthetized with halothane in oxygen-enriched air ($F\text{I}_{O_2}$=0.5) and Portex catheters (id 0.28 mm, od 0.61 mm) were implanted under aseptic surgical conditions into the lumbar subarachnoid space to lie next to the most caudal segments of the spinal cord, as described previously.[10] A minimum period of 18 h elapsed between catheter implantation and nociceptive testing. One experiment was performed on each animal per day up to a permitted maximum of six experiments.

NOCICEPTIVE TESTS

The electrical current threshold for nociception (ECT) was measured in the skin of the neck and tail every 5 min, as described previously.[10] The standardized response (*r*) was calculated by dividing the three ECT readings obtained 5, 10 and 15 min after intrathecal injection by the three pre-injection readings. In some experiments the tail flick latency (TFL) test was also used. In those experiments TFL

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was always measured 10–15 s before the ECT test was performed, as described previously.[10] The response to the intrathecal drugs was then calculated:

$$\%\text{MPE}=\frac{\text{mean TFL post-drug}-\text{mean TFL pre-drug}}{\text{cut-off time}-\text{mean TFL pre-drug}}\times 100$$

AGONIST DOSE–RESPONSE STUDIES

Dose–response relationships for a κ (U-50488H, Upjohn Ltd) and two δ (DSLET, RBI; DSBULET) opioid agonists were investigated. This was done in order to define doses of each agonist which produced just maximal, spinally mediated antinociceptive effects (maximum increase in the tail threshold with no increases in the neck threshold) and which were approximately equipotent with midazolam 46 nmol and fentanyl 0.74 nmol. These doses have been demonstrated previously to be equipotent and produce maximal spinally mediated antinociceptive effects.[10]

The responses (*r* values calculated as above) were combined for each dose of each agonist to calculate mean (SEM). Dose–response curves were plotted for each agonist and the dose of each agonist which produced a maximal increase in tail ECT with no change in the neck threshold was calculated.

In addition, the time course of the antinociceptive effect was examined for DSLET; electrical current thresholds in four animals who received intrathecal DSLET 9.1 nmol were measured for 40 min after intrathecal injection of drug. The nociceptive thresholds for each test were combined for each testing time between animals and plotted on a time–response curve.

EXPERIMENTS USING NOR-BINALTORPHIMINE

In this group of experiments each rat received intrathecal injection of an equipotent dose of agonist (U-50488H 210 nmol, midazolam 46 nmol or fentanyl 0.74 nmol) given alone at the beginning and again at the end of the series of experiments. Nociceptive thresholds were measured as above. These control responses obtained in the absence of any antagonist were pooled for each drug to derive a mean control agonist response to agonist alone (*R*). In addition, the pre- and post-series control responses for each agonist were compared statistically (Mann–Whitney *U* test) to test for drug tolerance or cumulative effects of antagonist. In the experiments intervening between the two control agonist responses, a range of doses of nor-binaltorphimine (0.0012–1.24 pmol), dissolved in saline, was injected, mixed with agonist, in the same intrathecal injection.

The responses to nor-binaltorphimine in suppressing the effects of all of these agonists were calculated as percentage suppression of control agonist response from the expression:

$$\%\text{suppression}=\frac{R-r}{R-1}\times 100$$

where R=mean control agonist response in the absence of antagonist and r=response to agonist in the presence of a particular dose of antagonist. The values obtained for each antagonist dose were combined to produce a mean (SEM) and plotted as antagonist dose–response curves.

EXPERIMENTS WITH NALTRINDOLE

In these experiments naltrindole 0.0011–11.1 nmol was given intrathecally dissolved in 5% glucose in a volume of 5 µl mixed with the agonists, and nociceptive thresholds were measured as above. The agonists used were fentanyl 0.74 nmol, U-50488H 210 nmol, DSLET 9.1 nmol, DSBULET 4 nmol and midazolam 46 nmol.

CONTROLS

Five rats with intrathecal catheters were given, on separate occasions, intrathecal naltrindole alone (11.1 nmol) and nor-binaltorphimine (1.24 pmol). The effects of these were assessed with both tests (ECT and TFL). These were the highest doses of antagonists used.

Baseline (pre-drug injection) values for tail nociceptive thresholds were compared with those obtained for the same animal on previous occasions in order to exclude changes induced by progressive neurological damage or residual drug effects. We did not perform control experiments for intrathecal saline alone (the vehicle for some drugs) as we have reported previously that this had no effect on nociceptive thresholds.[3] We did however perform control experiments in four animals who received 5 µl of intrathecal injections of 6% glucose solution which was the vehicle used for other drugs reported in this study.

STATISTICAL ANALYSIS

All data are shown as mean (SEM). Statistical comparisons were made using Mann–Whitney *U* tests. $P \leq 0.05$ was considered statistically significant.

Results

Evidence that the catheter was intrathecal (a positive lignocaine test) was obtained in all rats after all experiments. We compared the baseline ECT values in the tail for each animal at the beginning of each experiment and there was no change in thresholds over the course of the series which would have suggested neurological damage or residual drug effects. Also, there was no evidence of tolerance to drug effects from comparison of the responses to the same agonists obtained at the beginning and end of the series of experiments with each of the antagonists.

Table 1 Equipotent doses of U-50488H, DSLET and DSBULET derived from their dose–response relationships

Drug	Dose (nmol)	ECT (tail) (mean (SEM))	No. of experiments
U-50488H	210	1.55 (0.26)	11
DSLET	9.1	1.97 (0.23)	6
DSBULET	3.37	1.91 (0.28)	6

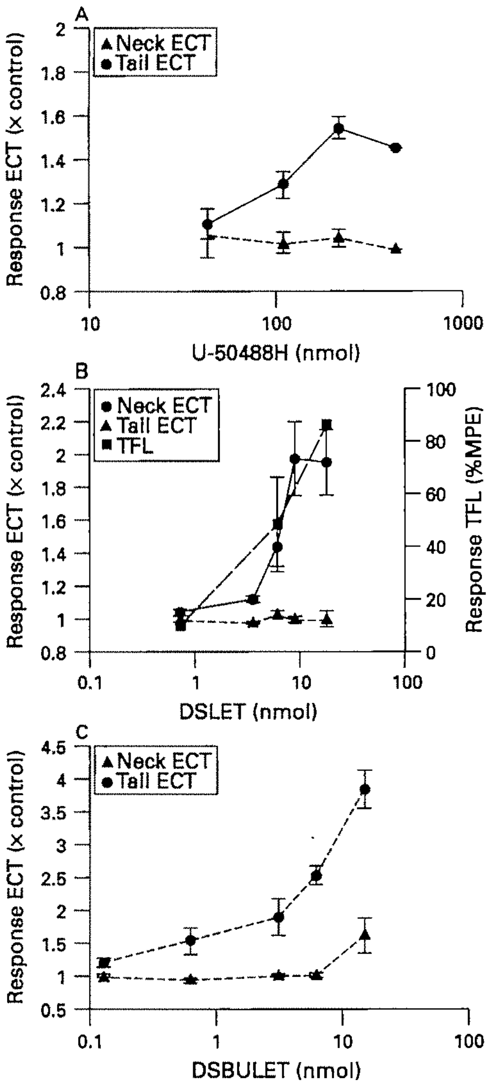

Figure 1 Dose–response curves for intrathecal U50488H (A), DSLET (B) and DSBULET (C) for neck and tail electrical current threshold (ECT) values and tail flick latency (TFL) (mean, SEM of 22 experiments in 13 rats (A), 31 experiments in six rats (B) and 30 experiments in six rats (C)).

AGONIST DOSE–RESPONSE STUDIES

All three opioids produced dose-dependent spinally mediated antinociception that was present and had a peak effect within 5 min (fig. 1). The doses of the three agonists, shown by these dose–response studies to produce just maximal segmental antinociceptive effects (increase in tail thresholds with no change in neck thresholds), are shown in table 1.

The antinociceptive effects assessed with the ECT for the δ and κ opioid agonists did not differ significantly from each other or from those obtained in the experiments with antagonists of midazolam (46 nmol; 1.81 (0.1) ECT tail) and fentanyl (0.74 nmol; 1.91 (0.07) ECT tail) (Mann–Whitney *U* test; $P > 0.1$). TFL was also measured in the experiments with DSLET. These measurements were performed only for doses of intrathecal DSLET of 0.728, 6.19 and 18.2 nmol. DSLET caused a dose-related increase in TFL.

Time–response curves were constructed from four experiments in four animals in the group that received DSLET and in six rats that received intrathecal DSBULET (fig. 2). Intrathecal DSLET 9.1 nmol produced an increase in the ECT in the tail with no change in the neck and this change occurred at 5 min and persisted for 20 min after injection and regressed towards control values during the following 20 min. Intrathecal DSBULET 3.37 nmol caused a sharp increase in the ECT in the tail with no change in the neck thresholds and this change in the tail was also stable for 15 min after injection.

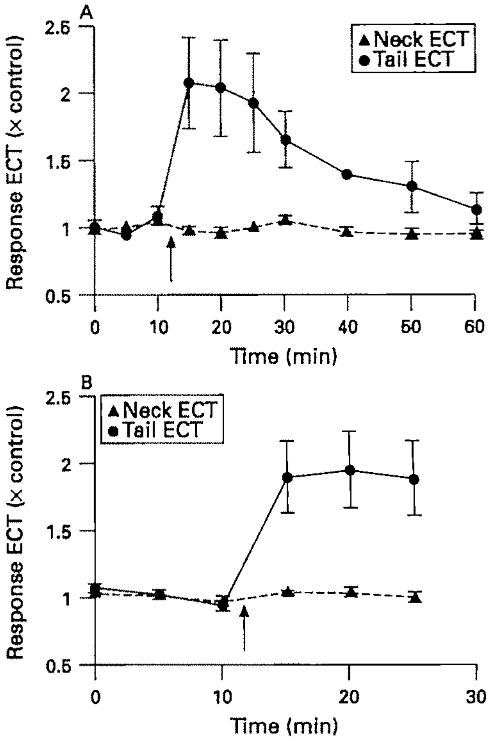

Figure 2 Time–response relationships for electrical current threshold (ECT) measurements after intrathecal DSLET 9.1 nmol ($n=4$ rats) (A) and DSBULET 3.37 nmol ($n=6$ rats) (B) (mean, SEM). Arrows indicate the time of intrathecal injection of drug.

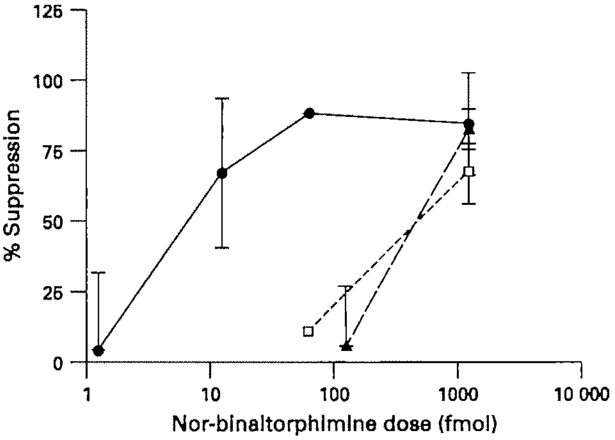

Figure 3 Nor-binaltorphimine dose–response curves for suppression of ECT antinociceptive effects of intrathecal midazolam 46 nmol (19 experiments, five rats) (▲), fentanyl 0.74 nmol (18 experiments, three rats) (□) and U-50488H 210 nmol (22 experiments, five rats) (●).

EXPERIMENTS WITH NOR-BINALTORPHIMINE

Nor-binaltorphimine dose–response curves for suppression of the antinociceptive effects of U-50488H,

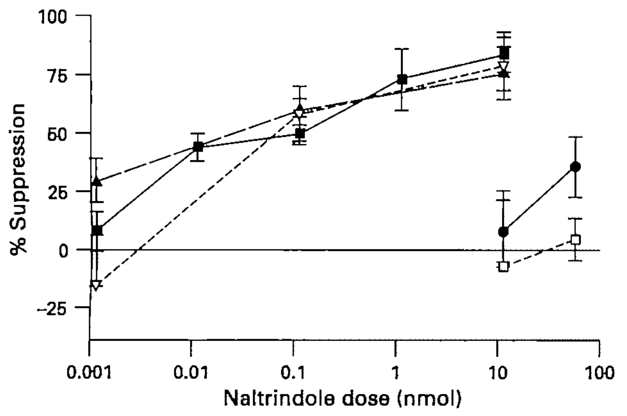

Figure 4 Naltrindole dose–response curves for suppression of ECT antinociceptive effects of intrathecal midazolam 46 nmol (16 experiments, eight rats) (▲), DSLET 9.1 nmol (24 experiments, eight rats) (■), DSBULET 4 nmol (16 experiments, four rats) (▽), fentanyl 0.74 nmol (eight experiments, eight rats) (□) and U-50488H 210 nmol (eight experiments, eight rats) (●). TFL measurements were also made in DSLET experiments but these are not shown for clarity because the naltrindole dose–response curve for suppressing this effect of DSLET is coincident with the curves for midazolam and the ECT effects of DSLET.

midazolam and fentanyl are shown in figure 3. The selective κ opioid antagonist suppressed only the antinociceptive effects of the κ opioid agonist U-50488H. There was 70% suppression of the effects of fentanyl and midazolam at the highest dose of norbinaltorphimine (i.e. 1.24 pmol); 5% of this dose (0.062 pmol) caused 100% suppression of the effects of U-50488H. Mean control responses before and after the experimental series to agonist alone were, respectively: U-50488H 1.62 and 1.57; midazolam 2.3 and 2.64; and fentanyl 2.14 and 2.08. There were no significant differences between the pre- and post-series controls for each drug (Mann–Whitney *U* test) indicating that no tolerance or cumulative drug effects had occurred.

EXPERIMENTS WITH NALTRINDOLE

Figure 4 shows naltrindole dose–response curves for suppression of the antinociceptive effects of all agonists tested. Naltrindole, a selective δ opioid antagonist, had no effect on fentanyl or U-50488H spinal antinociception at a dose of 11.1 nmol. In contrast, this dose of naltrindole produced highly significant suppression of spinally mediated antinociception caused by DSLET and DSBULET, the δ opioid agonists, and also midazolam. TFL results for DSLET are not shown in figure 4 in the interest of clarity. However, naltrindole 0.011 and 11.1 nmol caused 41.3 (19) % and 90.26 (10.6) % suppression of the TFL increases caused by intrathecal DSLET 9.1 nmol, the same dose–response relationship as that for suppression of the ECT effects of intrathecal midazolam and DSBULET. The dose–response curves for naltrindole antagonism of both δ opioid agonists and midazolam were coincident. The ED_{50} for this effect, that is the theoretical dose which would cause 50% suppression of spinally mediated antinociception, was the same for all three drugs (approximately naltrindole 0.5 nmol).

CONTROLS

ECT values in the tail were not changed in the four animals which received 5-μl injections of 6% glucose alone, indicating that this vehicle had no effect on nociceptive thresholds.

The pre and post-series control responses to agonist alone were: DSLET 1.97 (0.23) and 1.9 (0.18) ECT, 64.3 (13.3) and 74.7 (14.6) TFL; DSBULET 2.09 (0.07) and 2.09 (0.29) ECT.

Mean control responses to fentanyl and midazolam given alone were, respectively, 1.91 (0.07) and 1.8 (0.1). There were no significant differences between pre- and post-series control values for each δ opioid agonist given alone and there were no significant differences between control agonist responses, that is they were equipotent in causing spinally mediated antinociception and there was no evidence of tolerance to these agonists in this series of experiments.

Discussion

In the experiments reported here, we used two important principles to study the receptors responsible for spinally mediated antinociception caused by intrathecally administered agonists. First, in every experiment used for this analysis nociceptive thresholds in the tail increased after drug administration, with no change in neck thresholds. If drug is injected too rapidly intrathecally or at too large a volume, we have found previously that neck thresholds increase also. Second, traditionally, one analyses receptor subtypes using the technique described by Arunlakshana and Schild[11] to calculate the pA_2 value. In our experimental preparation the concentrations of agonist and antagonist are unknown and the system does not reach steady state, a requirement for pA_2 calculations.

Therefore, the technique of antagonist dose–response curve analysis was used in this as in previous studies.[3,5–7,12] This technique has since been verified by Mackay.[13,14] An antagonist dose–response curve describes the inter-relationship between the antagonist and a native receptor if this receptor causes a physiological effect by binding with exogenous drug or endogenous neurotransmitter. Thus the same antagonist dose–response curve with the same ED_{50} is obtained with a particular antagonist, suppressing the effects of two different drugs, whether they bind to the same receptor, or if one or both causes the release (directly or indirectly) of an endogenous agonist which then binds to the same receptor as the antagonist to produce the effect.

Previous experiments with naloxone indicated that intrathecal midazolam activated a spinal opioid system.[5,8] Benzodiazepine antinociception is probably not a μ opioid effect as fentanyl spinal antinociceptive effects were more sensitive to suppression by naloxone than those of either ketocyclazocine (the archetypal κ opioid agonist) or midazolam[5,8] and naloxone has been shown to display some selectivity for the μ receptor.[15] Although ketocyclazocine is the archetypal κ opioid it is not very selective. However, other studies indicated that a κ opioid ligand with higher selectivity for the κ opioid receptor than ketocyclazocine, ICI 197067, had a similar ED_{50} for naloxone suppression of its spinally mediated antinociceptive effects.[16] Although naloxone is more selective for the μ opioid receptor, the degree of selectivity is not high and it does not discriminate between δ and κ opioid sites. Clearly further experiments with more selective antagonists are needed. This study demonstrated a very high degree of selectivity for nor-binaltorphimine for antagonism of the effects of the κ opioid agonist U-50488H compared with the μ opioid agonist fentanyl. Spinal antinociception produced by midazolam was not suppressed by the doses of nor-binaltorphimine which were selective for the μ opioid receptor, although some suppression was produced by the higher, non-selective doses of nor-binaltorphimine which also suppressed fentanyl antinociceptive effects.

Naltrindole showed a high degree of selectivity for the δ opioid receptor. Suppression of spinal antinociception caused by the δ selective opioid agonists, DSLET and DSBULET, occurred over a range of doses of naltrindole which were three or four orders of magnitude less than those which caused small amounts of suppression of responses to fentanyl and U-50488H. The naltrindole dose–response curve for suppression of antinociception produced by midazolam was to the left of the curves for the κ and μ opioids and it is coincident with all the curves for suppression of the effects of the selective δ opioid agonists. It may be concluded that intrathecal midazolam produces antinociception by activating a system which involves δ opioid receptors. Furthermore, this system is confined to the spinal cord because all experiments in this study demonstrated a differential effect on tail thresholds, that is tail thresholds increased, with no change in ECT occurring in the neck and thus all drug effects and interactions between agonist and antagonist must have occurred at the spinal cord level. It is clear that the initial step in this process is combination of the drug with a typical $GABA_A$/BZ receptor complex as both bicuculline, a $GABA_A$ antagonist, and flumazenil, a benzodiazepine receptor antagonist, suppressed midazolam spinally mediated antinociception in a dose-related manner.[5 6] However, flumazenil and bicuculline did not block the spinal analgesic effect of μ, κ or δ opioid agonists.[17 18] Therefore, the results indicate that intrathecal midazolam positively modulates the effect of GABA at $GABA_A$ receptors and the effect of this is to cause the release of an endogenous opioid acting at δ opioid receptors. It is not known if these $GABA_A$/BZ receptors are pre- or postsynaptic and on what neuronal elements in the spinal cord they are located. However, the effect of positive modulation of GABA at these receptors is to increase chloride flux into the neurone, thus inhibiting its firing. Thus the effect would be to decrease neurotransmitter release from a presynaptic terminal or postsynaptic cell. We must therefore conclude that the pre- or postsynaptic effect leads to decreased release of an inhibitory neurotransmitter that normally inhibits the neuronal release of an opioid acting at δ opioid receptors.

It has been shown previously that intrathecal midazolam 46 nmol increases ECT values without affecting TFL.[10] There have been reports of TFL increases and mixed antinociceptive and hyperalgesic effects after administration of midazolam.[19] However, studies using the preparation that we used in which tail and neck ECT values were measured have consistently demonstrated increases in tail ECT with no change in TFL or neck ECT in the same experiments.[10] The possibility exists in other studies for spread of drug to the brain and that these supraspinal actions lead to mixed effects and TFL increases.

The dose of midazolam (46 nmol) used in these studies produced spinally mediated antinociception measured by the ECT test and was equipotent with doses of fentanyl and DSLET. However, the δ opioid agonist also caused an increase in TFL and increases in ECT values. This TFL effect must be mediated by a spinal cord mechanism as increases in TFL occurred after intrathecal DSLET at doses which caused increases in ECT in the tail without any change in the neck thresholds. We conclude that these two antinociceptive effects of the δ opioid are mediated by separate spinal cord mechanisms. The first (revealed by the ECT test) may be activated by intrathecal benzodiazepine causing the release of an endogenous δ opioid. The second (revealed by the TFL test) may be activated by exogenous δ opioids or endogenous opioid peptides selective for δ opioid receptors but not those released by midazolam.

These results provide further evidence that intrathecal midazolam produces antinociceptive effects by interactions with spinal systems. There may be useful potentiation of antinociceptive and analgesic effects to be gained by concurrent therapy with a μ selective opioid and midazolam. This suggestion, based on the results presented here, is supported by other studies in rats.[4] These authors reported potentiation of submaximal doses of intrathecal morphine by intrathecal injections of midazolam in the tail flick test. This additive effect is interesting because midazolam alone does not increase TFL, concurring with observations reported previously.[10] The mechanism of this interaction is unknown but the results reported here showed intervening steps involving the release of endogenous neurotransmitter substances. These may be the source of that interaction and potentiation, although more work needs to be performed to verify this suggestion.

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References

1. Cripps TP, Goodchild CS. Intrathecal midazolam and the stress response to upper abdominal surgery: adrenocortical, glycemic, and analgesic effects. *Clinical Journal of Pain* 1988; 4: 125–128.
2. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man—a pilot

study. *British Journal of Clinical Pharmacology* 1987; **23**: 273–285.

3. Goodchild CS, Serrao JM. Intrathecal midazolam in the rat: evidence for spinally-mediated analgesia. *British Journal of Anaesthesia* 1987; **59**: 1563–1570.
4. Yanez A, Sabbe MB, Stevens CW, Yaksh TL. Interaction of midazolam and morphine in the spinal cord of the rat. *Neuropharmacology* 1990; **29**: 359–364.
5. Boulter N, Serrao JM, Gent JP, Goodchild CS. Spinally mediated antinociception following intrathecal chlordiazepoxide—further evidence for a benzodiazepine spinal analgesic effect. *European Journal of Anaesthesiology* 1991; **8**: 407–411.
6. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. *Anesthesiology* 1990; **73**: 273–277.
7. Nadeson R, Goodchild CS. The effect of $GABA_A$ antagonists SR95531 and bicuculline on spinal antinociception induced by midazolam, 5-HT, muscimol and GABA in rats. *Canadian Journal of Physiology and Pharmacology* 1994; **72**: 345.
8. Serrao JM, Goodchild CS, Gent JP. Reversal by naloxone of spinal antinociceptive effects of fentanyl, ketocyclazocine, and midazolam. *European Journal of Anaesthesiology* 1991; **8**: 401–406.
9. Singh L, Field MJ, Vass CA, Hughes J, Woodruff GN. The antagonism of benzodiazepine withdrawal effects by the selective $cholecystokinin_B$ receptor antagonist CI-988. *British Journal of Pharmacology* 1992; **105**: 8–10.
10. Serrao JM, Stubbs SC, Goodchild CS, Gent JP. Intrathecal midazolam and fentanyl in the rat: evidence for different spinal antinociceptive effects. (Published erratum appears in *Anesthesiology* 1989; 71: 482.) *Anesthesiology* 1989; **70**: 780–786.
11. Arunlakshana O, Schild HO. Some quantitative uses of drug antagonists. *British Journal of Pharmacology* 1959; **14**: 48–58.
12. Guo Z, Gent JP, Goodchild CS. Two GABA mechanisms for spinally-mediated antinociception: evidence from antagonism of 5-hydroxytryptamine (5HT) by bicuculline. *British Journal of Anaesthesia* 1990; **64**: 589P–590P.
13. Mackay D. Receptor classification using antagonists. *Trends in Pharmacological Sciences* 1991; **12**: 181.
14. Mackay D. A new method for estimating dissociation constants of competitive and non-competitive antagonists with no prior knowledge of agonist concentrations. *British Journal of Pharmacology* 1994; **111**: 219–226.
15. Yaksh TL. Spinal opiates: a review of their effect on spinal function with emphasis on pain processing. *Acta Anaesthesiologica Scandinavica Supplement* 1987; **85**: 25–37.
16. Goodchild CS, Sanghera S, Serrao JM, Gent JP. Analgesia mediated by spinal κ-opioid receptors. *European Journal of Anaesthesiology* 1991; **8**: 227–231.
17. Serrao JM. Evaluation of drugs to be used for spinal analgesia. PhD thesis. Leeds: University of Leeds, 1992.
18. Guo Z. The mechanisms of the antinociceptive effects of intrathecally administered 5- hydroxytryptamine and xylazine in the spinal cord. PhD thesis. Leeds: University of Leeds, 1991.
19. Niv D, Davidovich S, Geller E, Urca G. Analgesic and hyperalgesic effects of midazolam: dependence on route of administration. *Anesthesia and Analgesia* 1988; **67**: 1169–1173.

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A model of the first pass passage of drugs from i.v. injection site to the heart—parameter estimates for lignocaine in the sheep

R. N. UPTON

Summary

A general model, based on indicator dilution principles, of the initial distribution and effects of drugs in a target organ after i.v. bolus administration is presented. The model was validated from previous studies of myocardial pharmacokinetics and pharmacodynamics of lignocaine in sheep. It is proposed that i.v. drug injection produces a concentration "peak" of drug in venous blood, which is attenuated by vascular mixing, and lung and heart kinetics, as the drug is transported from the injection site to the heart where it exerts its effects. The model predicted that the first passage of this peak through the heart was the principal component of myocardial concentrations of lignocaine for 10 min after injection before recirculation became important. Injection rate, cardiac output and myocardial blood flow were important determinants of the magnitude of the first pass peak. The model provides a physiological framework for analysing the initial distribution of drugs. (*Br. J. Anaesth.* 1996; **77**: 764–772)

Key words
Pharmacokinetics, models. Liver, metabolism. Anaesthetics local, lignocaine. Sheep.

Drugs that have direct effects on the heart (such as i.v. anaesthetics, anti-arrhythmics, analgesics and sedatives) are often administered as an i.v. bolus in anaesthesia and critical care medicine. After this type of administration, the time courses of both therapeutic and adverse effects change rapidly in the first 10 min after injection.[1 2] As a generalization, clinical practice has empirically evolved dose regimens that minimize adverse effects by matching the dose and rate of injection of a drug to the pathophysiological state of the patient, but the physiological basis of the dose regimens is often poorly understood.[1] While studies of the pharmacokinetics of these drugs in systemic blood provide some insight, evidence is accumulating that the time course of many of the direct myocardial effects in the period immediately after bolus administration are related closely to the time course of their concentration in the heart.[3 4]

It has been increasingly recognized that the conventional one-, two- or three-compartment interpretation of bolus kinetics (for example, see Gibaldi and Perrier[5] and Wood[6]) is not well suited to the description of the initial kinetics of drugs administered as i.v. boluses.[7 8] Limitations include poor description of vascular mixing,[9] poor description of lung kinetics[7 10] and in the case of cardioactive drugs, poor description of the time course of myocardial drug concentrations, and their determinants, in the period immediately after a drug bolus.[1 11]

The origin of many of these limitations may be traced to the assumption that drug is added instantly to an initial distribution volume with little or no anatomical basis. Although the concept of an initial distribution volume is widespread in the literature, in reality, a bolus dose of a drug is added to a stream of flowing blood, which mixes with other blood in the venous "tree", passes through the lungs and enters the organs of the body, including the heart, where it exerts its effects. The aim of this article is to develop a physiologically realistic model of this process based on indicator dilution principles, and to examine the predicted determinants of initial myocardial drug concentrations and effects after bolus administration. The validity of each component of the model is examined by comparison with a detailed set of physiological data from previously published experiments on myocardial pharmacokinetics and pharmacodynamics of lignocaine using a chronically instrumented sheep preparation.

AN "INDICATOR DILUTION" INTERPRETATION OF BOLUS KINETICS

The conventional compartmental approach to bolus kinetics recognizes that there is an initial period of "intravascular mixing" of drug with blood after bolus injection, but this process is generally ignored. However, the mechanisms of this process are well understood and can be described by indicator dilution principles[12] developed for the measurement of blood flow. For example, a classical method for measuring cardiac output is based on injection of indocyanine green (ICG) into the stream of venous blood flowing to the heart. A hypothetical "dye curve" in the blood downstream from the injection site (e.g the aorta) is shown in figure 1. Note that the

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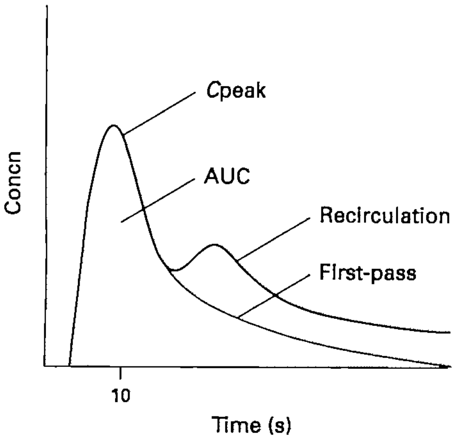

Figure 1 A hypothetical indicator dilution measurement of cardiac output. The first pass area under the curve (AUC) and peak concentration (*C*peak) are functions of cardiac output.

ICG concentration is initially zero, that there is a short lag between injection and first detection of ICG in blood, that there is a peak concentration (*C*peak), and that there is often a second peak because of recirculation of ICG. For flow measurements, various techniques are used to subtract the contribution of recirculation, leaving the first pass peak shown in figure 1, and cardiac output is determined from dose and the AUC of this peak. By rearranging the formula for cardiac output,[12] it is apparent that *C*peak is some function (f) of dose and cardiac output (Q_T).

$$C\text{peak}=f\,(\text{dose}/Q_T) \qquad (1)$$

In this article this indicator dilution analysis is expanded to examine the determinants of the shape of this peak for the first pass passage of a drug from the venous injection site to the heart. A central hypothesis is that although these indicator dilution principles are only applicable over a period of less than 30 s for an intravascular indicator such as ICG, they are applicable over a larger time scale for drugs that can leave the vascular space.

Methods

DEVELOPMENT OF THE MODEL AND PARAMETER ESTIMATION

On anatomical and theoretical grounds, the injected drug peak would be expected to pass though several sites in its passage to the target organ. These sites, together with the factors which could modify the shape of the peak at each site, are summarized in figure 2 and are examined in turn (with the sites referred to by a letter for direct comparison with fig. 2).

In common with all physiological models, this model is highly dependent on estimation of the large number of parameters comprising the model. For the purpose of illustration, these parameters were estimated for the local anaesthetic and anti-arrhythmic lignocaine, with the heart as the target organ, from previously reported studies of lignocaine using a conscious chronically instrumented sheep preparation.[2 4 13–15] Lignocaine causes significant reductions in myocardial contractility by a direct action on the myocardium,[16] probably by a direct action on Na–Ca exchange.[17]

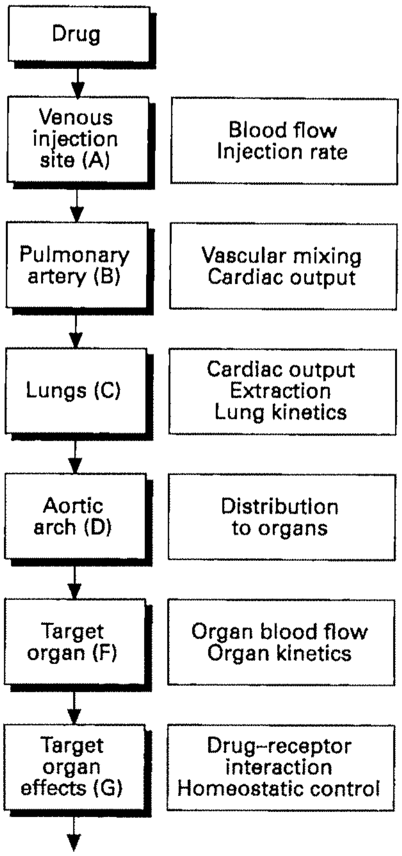
Drug
Venous injection site (A)
Blood flow Injection rate
Pulmonary artery (B)
Vascular mixing Cardiac output
Lungs (C)
Cardiac output Extraction Lung kinetics
Aortic arch (D)
Distribution to organs
Target organ (F)
Organ blood flow Organ kinetics
Target organ effects (G)
Drug–receptor interaction Homeostatic control

Figure 2 An overview of the processes affecting the shape of a first pass drug peak from the venous injection site to a target organ. The panels on the left indicate the site of the various processes, while the panels on the right indicate the most important determinants of the process. The letters in brackets correspond to the appropriate sections in the text.

A. Venous injection site

General form. It was assumed that for an i.v. bolus, the dose is injected at a constant rate over a period T. The dose rate (given the variable name Doserate) is therefore as follows, where dose=total mass of drug given and t =time after the start of the dose:

$$\text{Doserate}=(\text{dose}/T) \quad \text{for } 0\leqslant t\leqslant T \qquad (2)$$

It was assumed that drug injection gives a square wave drug concentration peak in blood (*C*inj) immediately downstream of the injection site, whose shape depends on local blood flow (Qinjsite) and the dose rate:

$$C\text{inj}=(\text{Doserate}/Q\text{injsite}) \quad \text{for } 0\leqslant t\leqslant T \qquad (3)$$

This is a direct application of indicator dilution principles—the higher the flow, the lower *C*inj, and vice versa.[12]

Parameter estimates for lignocaine. A dose of 100 mg over 1 s was assumed for comparison with previously published work,[2 4 14] and the injection was assumed to be made into the caudal end of the inferior vena cava, with a flow of 1 litre min^{-1} (Upton RN, unpublished observations).

B. Vascular mixing and dilution with cardiac output

General form. After injection, this hypothetical square wave was assumed to travel from the injection site to the pulmonary artery, with two factors influencing its shape in transit. The first is progressive dilution with other venous blood until, by the pulmonary artery, the peak has been diluted with the entire cardiac output (Q_T). Assuming it is still in the form of a square wave and ignoring the time taken to travel from the injection site to the pulmonary artery, this concentration (Cunmixed) is given by the following equation, analogous to equation (3):

$$C\text{unmixed} = (\text{Doserate}/Q_T) \quad \text{for } 0 \leq t \leq T \qquad (4)$$

However, in reality, as shown in figure 1, the shape of this peak is not a square wave, but has been modified by factors such as dispersion during transit along the vessel[18] and the dynamics of the mixing process. It was assumed that these two processes occur sequentially, and that the shape of the peak after dispersion was equivalent to the passage of the square wave peak created by the first process (eqn (4)) through a small well mixed compartment through which the entire cardiac output flowed. The final concentration in the pulmonary artery (Cpa) was therefore given by the following equation, where Vmix was the volume of this hypothetical mixing compartment:

$$dC\text{pa}/dt = (Q_T/V\text{mix}) \times (C\text{unmixed} - C\text{pa}) \qquad (5)$$

Parameter estimates for lignocaine. A baseline value for cardiac output (Q_T) of 5.6 litre min^{-1} was assumed for comparison with previously published work.[2] The volume of the mixing compartment was estimated from studies of the time course of ICG concentrations in the pulmonary artery for various combinations of injection duration and cardiac output[19] using hybrid physiological modelling (appendix).

C. Passage through the lungs

General form. The kinetics of the passage of the peak through the lungs was represented as a single flow-limited compartment through which cardiac output flowed. An extraction term (Elung) was included to account for any metabolism or prolonged retention of drug in the lung. The resultant drug concentrations in arterial blood emerging from the lungs (Ca) were therefore given by the following equations, where Vlung=apparent volume of the lung and Ca′=a temporary variable:

$$dC\text{pa}/dt = (Q_T/V\text{lung}) \times (C\text{pa} - C\text{a}')$$
$$C\text{a} = C\text{a}'(1 - E\text{lung}) \qquad (6 \text{ and } 7)$$

Parameter estimates for lignocaine. Vlung and Elung were determined by hybrid physiological modelling (appendix) from studies using chronically instrumented sheep in which arterial blood was sampled rapidly together with measures of cardiac output.[14] Arterial drug concentrations in the first minute after injection were assumed to be a result of the first pass passage of the drug, and pulmonary artery concentrations were determined by application of the vascular mixing algorithm (eqns (2–5)).

D. Distribution to organs

Emerging from the lungs in arterial blood, the peak is distributed to all organs of the body (except the lung and those supplied by portal systems) in line with the fraction of cardiac output they receive. As outlined previously, this model addresses only the relevant target organ, as the fate of the drug in other organs does not influence the first pass peak in this organ.

F. Target organ kinetics

General form. The kinetics of the passage of the peak through the target organ was represented as a two-compartment model with membrane limited transfer from the first (nominally capillary) to the second (nominally parenchymal) compartment, where the transfer between the compartments was described by a permeability term (PS) in keeping with standard capillary permeability nomenclature.[20] If Qorgan is the blood flow of the target organ, and Vcap and Vpar are the apparent volumes of the nominal capillary and parenchymal compartments (concentrations Ccap and Cpar, respectively), the equations describing this system were as follows:

$$V\text{cap}\,(dC\text{cap}/dt) = Q\text{organ}\,(C\text{a} - C\text{cap}) + \text{PS}\,(C\text{par} - C\text{cap})$$
$$V\text{par}\,(dC\text{par}/dt) = \text{PS}\,(C\text{cap} - C\text{par}) \qquad (8 \text{ and } 9)$$

The advantage of this model is that a single-compartment, flow-limited model is a subset of its solution if PS is greatly exceeds Qorgan.

Parameter estimates for lignocaine. These were determined by hybrid physiological modelling (appendix) of studies with chronically instrumented sheep in which arterial (afferent for the heart) and coronary sinus (efferent) blood were sampled rapidly, in conjunction with measures of myocardial blood flow using an ultrasonic Doppler flow probe on the left mainstem coronary artery.[2] Initial trials showed a single flow-limited compartment model was preferred statistically, but was modified by the addition of a small first-order loss from the compartment (rate constant=k_{out}), which further improved the fit. Equation 8 was therefore modified as follows:

$$V\text{m}\,(dC\text{m}/dt) = Q\text{m}\,(C\text{a} - C\text{m}) - k_{\text{out}} \times C\text{m} \qquad (10)$$

where Vm and Cm =apparent volume of, and concentration in, the heart, respectively. Note that the heart concentrations of this equation are equivalent to those in the coronary sinus, that is there is venous equilibrium).

G. Target organ dynamics

General form. The relationship between the target organ drug concentration and a drug effect in that organ (Eorgan) was represented by a sigmoidal Emax relationship,[21] where Emax=maximum drug effect and EC_{50}=drug concentration at which 50% of Emax was achieved, n="Hill factor" controlling the steepness of the sigmoidal curve and "baseline" is the predrug magnitude of the effect:

$$E\text{organ} = ((E\text{max} \times C\text{organ}^n)/(\text{EC}_{50}{}^n + C\text{organ}^n)) + \text{baseline} \qquad (11)$$

This equation can describe several concentration effect relationships, as it includes linear and Emax models as approximate subsets of its solutions, and the organ concentration can be for either the capillary or parenchymal compartments.

Parameter estimates for lignocaine. These were determined using hybrid physiological modelling (appendix) of studies in which myocardial contractility and coronary sinus blood concentrations of lignocaine were determined after bolus injection of lignocaine in sheep.[4 14] Contractility was determined from the maximum rate of rise of left ventricular pressure (LV (dP/dt)max), which was measured using a left ventricular micromanometer catheter, and was expressed as the percentage reduction from baseline values. Initial trials showed that the sigmoid *E*max model had redundant parameters for this data set, and it was replaced with a linear effect model modified for a drug which caused reductions in the effect from a baseline value:

$$Em = \text{baseline}_{\text{eff}} - \text{slope}_{\text{eff}} \times Cm \qquad (12)$$

where *E*m=percentage reduction in myocardial contractility.

Equation solving

The model, as implied by equations (2–7), (10) and (12) was implemented as a set of differential equations in the "Scientist" modelling package (Scientist for Windows, Version 2, Micromath, Salt Lake City, UT, USA), although any differential equation solver would be suitable. In general terms, the model could be used to predict the shape of the peak at each of the sites shown in figure 2, and the resultant time course of a drug effect. Equation (3) is optional, and can be included if venous injection site concentrations are of interest.

Predictions of the model. The model was used to predict the peak first pass concentrations of lignocaine, and the times of these peaks, in venous, pulmonary artery and arterial blood and the heart after an injection of 100 mg over 30 s.

To examine to what extent the first pass peak contributed to initial distribution *in vivo*, the predictions of the model were compared with the experimental data reported previously for lignocaine pharmacokinetics and pharmacodynamics in the heart.[4 14] The former accounted only for the first pass passage of the drug peak, while the latter *in vivo* measurements by definition included the first pass peak and the contribution of recirculation.

The sensitivity of the model to changes in various parameters was also analysed. Of the parameters shown in figure 2, it was thought that injection rate, cardiac output and target organ blood flow were the parameters that were most likely to vary in a "clinical" setting. The effect of changing these was summarized concisely by their effect on the coronary sinus concentrations alone as the simple linear nature of the pharmacodynamic model (eqn (12)) implies that the effect follows the same time course as the coronary sinus concentrations, and the kinetic model for the heart (eqn (10)) implies that the heart concentrations were proportional to the coronary sinus concentrations. To examine the effect of blood flow, cardiac output was increased or decreased by 50% (from 5.6 to 8.4 and 2.8 litre min^{-1}, respectively). In a separate set of simulations, myocardial blood flow was increased or decreased by 50% (from 0.122 to 0.183 and 0.061 litre min^{-1}, respectively). In a final set of simulations, cardiac output and myocardial blood flow were increased together by 50%, and then decreased together by 50%. To examine the effect of injection rate, simulations were performed with the duration of injection set at values of 1, 10, 30, 60, 120 or 240 s.

Results

PARAMETER ESTIMATES FOR LIGNOCAINE

The values of the parameters of the model are summarized in table 1; all estimated parameters were determined with a high degree of confidence. Although the vascular mixing component of the model was entirely empirical, there was good agreement between the model and the published data,[19] as shown in figure 3. The parameters for lung kinetics gave a good description of the observed arterial concentrations emerging from the lung (fig. 4), but the fit was improved by removing a small (0.08 min) lag from the measured concentrations consistent with previous observations of injection site to lung transit time.[19] The membrane-limited model of the target organ collapsed to a single-compartment, flow-limited model on fitting. This latter model was able to describe coronary sinus concentrations within the confidence limits of the measured data; a better fit was obtained by adding a small first-order loss from the compartment (fig. 5). This may have a physiological basis, as loss of lignocaine from the surface of the heart into fluid (and presumably tissues) surrounding the heart has been documented.[22] The linear pharmacodynamic model gave an adequate description of the relationship between the measured coronary sinus concentration and effect data (fig. 6).

Table 1 Parameters of the model for lignocaine in the heart

Parameter	Description	Value used (SD)	Source
Dose	Total dose	100 mg	Assumed
T	Duration of injection	1 s	Assumed
$\dot{Q}$inj	Local blood flow at the injection site	1 litre min^{-1}	Assumed
$\dot{Q}$T	Cardiac output	5.6 litre min^{-1}	Measured directly
*V*mix	Volume of the hypothetical venous mixing compartment	0.255 litre	Hybrid modelling
*V*lung	Apparent volume of the lung	1.06 (0.021) litre	Hybrid modelling
*E*lung	Apparent first pass extraction by the lung	0.32 (0.03)	Hybrid modelling
$\dot{Q}$m	Blood flow through heart	0.122 (0.021) litre min^{-1}	Measured directly
*V*m	Apparent volume of the heart	0.450 (0.03) litre	Hybrid modelling
*k*out	First order loss rate constant from the heart	0.062 (0.04) litre min^{-1}	Hybrid modelling
$\text{Slope}_{\text{eff}}$	Slope of linear pharmacodynamic model	11.08 (0.56)	Hybrid modelling
$\text{Baseline}_{\text{eff}}$	Baseline of linear pharmacodynamic model	3.16 (1.17)	Hybrid modelling

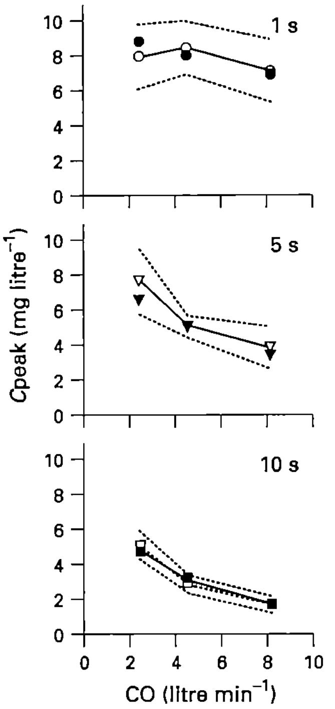

Figure 3 Predictions of the venous mixing component of the model (eqns (2–5)) using a value of *V*mix of 255 ml compared with the observations of Upton and Huang[19] on the initial mixing of indocyanine green with venous blood. The panels show the relationship between peak concentration (*C*peak) and cardiac output (CO) for injections rates of 1 s (top), 5 s (middle) and 10 s (bottom). Similar results were also found for the area under curve of the peak. In each case, the open symbols indicate the observed values, the dashed lines their 95% confidence limits and the filled symbols, predicted values.

PREDICTIONS OF THE MODEL

The major prediction of this model was that bolus drug injection produces a large concentration peak in venous blood which is progressively attenuated by various kinetic processes in transit to the target organ (table 2). It was also shown that the predicted first pass peak contributed a large component to the experimentally determined coronary sinus lignocaine concentrations (and therefore myocardial effect) in the first 10 min after the dose (fig. 7). Of the parameters examined, changes in cardiac output alone produced the largest changes in peak coronary sinus concentrations (fig. 8), with the highest cardiac output associated with the lowest concentration. Conversely, changes in myocardial blood flow alone also produced large changes in peak coronary sinus concentrations (fig. 8), but with the highest flow associated with the highest concentration. When cardiac output and myocardial blood flow were increased or decreased simultaneously, the opposing factors were cancelled such that there was a less dramatic change in coronary sinus concentrations (fig. 8). However, the lower flow state was associated with a longer duration of action and a slight delay in the time of the maximum concentration. Altering injection rate from 1 to 240 s produced large changes in coronary sinus concentrations (fig. 9), but for injection rates in the range 1–30 s, the changes were only minor.

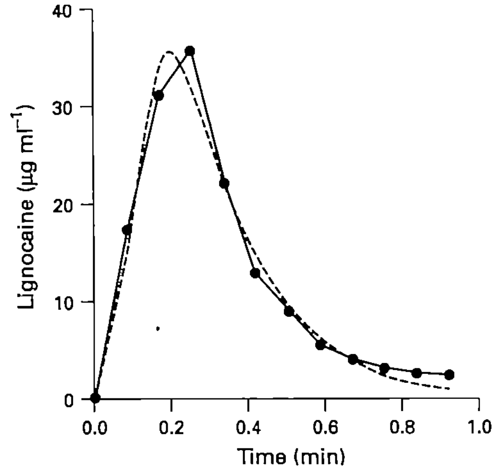

Figure 4 Predicted (—) first pass arterial concentrations of lignocaine (based on eqns (2–7)) emerging from the lungs in the first minute compared with those measured *in vivo* by Huang and colleagues (●).[14]

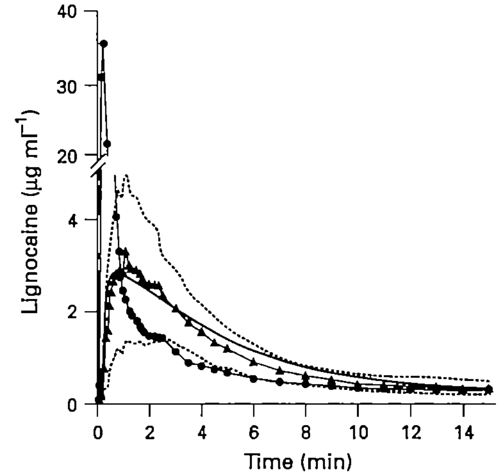

Figure 5 Predicted (–) coronary sinus concentrations of lignocaine based on equation (10) compared with those measured by Huang and colleagues[14] (▲) shown with their 95% confidence limits (dotted lines). Measured arterial concentrations (●) are shown for comparison.

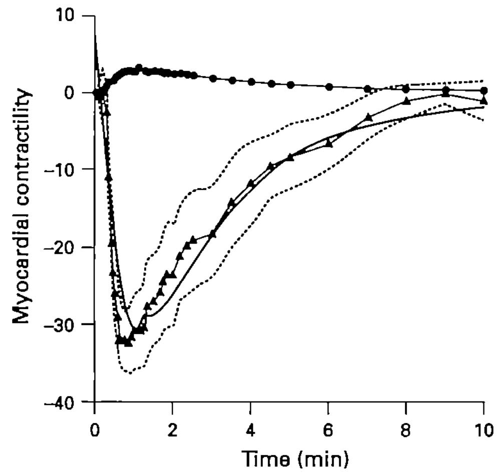

Figure 6 Predicted (–) effect of lignocaine on myocardial contractility (reduction from baseline) based on equation (12) compared with that measured by Huang and colleagues[4] (▲) shown with their 95% confidence limits (dotted lines). Measured coronary sinus concentrations (●) are shown for comparison. The units of the vertical axis are arbitrary.

Table 2 Peak first pass concentrations of lignocaine at various sites after injection of 100 mg over 30 s

Site	Peak concentration (mg litre^{-1})	Time of peak (min)
Venous injection site	35.7	0–0.5
Pulmonary artery	35.7	0.5
Aorta	22.1	0.5
Heart	2.6	0.9

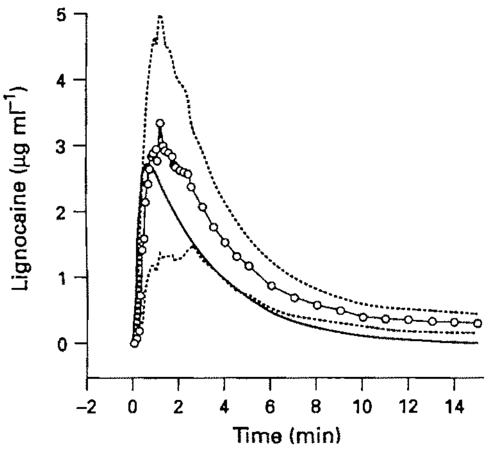

Figure 7 Predicted (–) first pass peak of lignocaine in coronary sinus blood after i.v. injection of 100 mg over 1 s compared with measured concentrations (○) and 95% confidence limits (dotted lines), which by nature includes the contribution caused by recirculation. The first pass peak makes a large contribution to the heart concentrations of lignocaine in the first 10 min after injection.

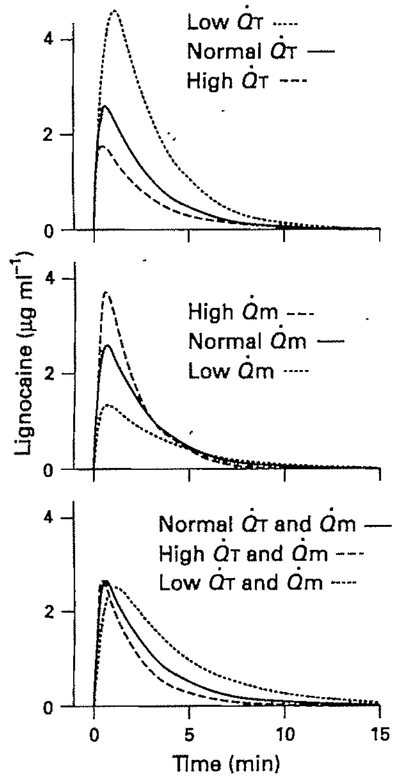

Figure 8 Effect of cardiac output (Q_T) and myocardial blood flow (Q_m) on the first pass peak of lignocaine in the heart, as given by coronary sinus blood concentrations. The upper panel shows Q_m held constant, with 50% increases or decreases in Q_T. The middle panel shows Q_T held constant, with 50% increases or decreases in Q_m. The lower panel shows Q_T and Q_m varying in unison.

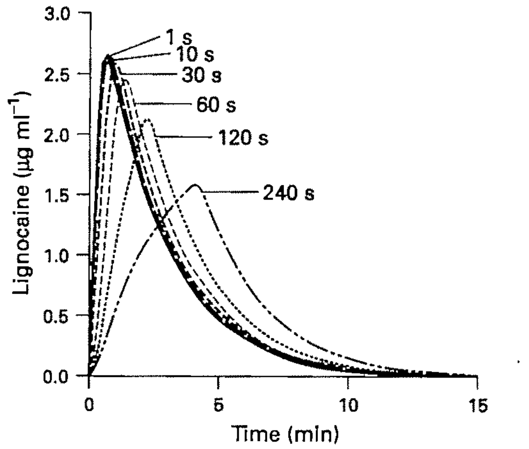

Figure 9 Effect of altering duration of injection of the same dose of lignocaine on its first pass peak in the heart, as given by coronary sinus blood concentrations.

Discussion

It was shown that initial drug kinetics after an i.v. bolus injection were consistent with the concept of the formation of a concentration "peak" of drug in the flow of venous blood, which is attenuated by vascular mixing, and lung and target organ kinetics as the drug is transported from the injection site to the target organ. The first passage of the peak through the heart was the principal component of the myocardial concentrations of lignocaine for 10 min after injection. Injection rate, cardiac output and myocardial blood flow were important determinants of the first pass peak. While there are deficiencies in the model, it is clear that it provides a useful framework for studying initial distribution processes and their physiological determinants.

OTHER APPROACHES TO INITIAL DRUG DISTRIBUTION

The limitations in the interpretation of the initial distribution volume and half-life terms of conventional compartmental models have been raised by previous workers. Chiou[7 8] showed the initial volume of distribution depended on the time that the first blood sample was obtained (i.e. the time allowed for "initial mixing"), and that there was considerable variation in the literature of the reported initial volume of distribution for the same drug. Indeed, the initial volume was related linearly to the time of the first blood sample. The role of the lung in first pass kinetics was also considered by this author.

There have been three general approaches to addressing these limitations, which will be discussed in turn. First, some workers have developed revised compartment models. Niazi[23] advanced the concept of volume of distribution as a variable that changes with time. However, the fundamental compartmental description of a drug added to a volume rather than a flow remains. By rapid sampling of arterial blood from 1 min after injection of thiopentone and an intravascular marker, Henthorn, Avram and Krejcie[24] were able to show that thiopentone and the marker had a common central volume in humans.

Subsequent work in dogs with continuous sampling showed that this common volume was the first pass peak emerging from the lungs, and led to the construction of a physiological model of the process.[9 25] The vascular mixing component of this model is essentially the same as that proposed in the current model. They differ in that their model incorporates a two-compartment model of the remainder of the body, and was validated against arterial concentrations rather than target organ drug concentrations and effects. The model of early alfentanil disposition proposed by Wada and Ward[26] also shares similar features with the present model, and was validated by hybrid modelling of literature data.

Second, to avoid a compartmental description of the initial distribution process, stochastic recirculatory models of the process have been proposed.[27–30] This approach greatly improves the ability of these methods to describe early blood drug concentrations compared with compartmental models and includes the role of cardiac output in initial distribution. Some disadvantages include lack of a physiological description for the "transport function", validation against limited data sets, and neglecting the significant effect of cardiac output on the whole body transport function.

Third, there have been occasional theoretical and experimental reports of an indicator dilution approach to initial drug distribution in which the drug is considered to be added to a flow rather than a volume. The most significant theoretical contribution is that of Crawford.[31] It was proposed that rapid i.v. injection of a drug resulted in a "slug" of drug in blood which travelled for two or three circulations of the blood before being dispersed. In his analysis, Crawford essentially analysed the fate of the slug at each of the sites shown in figure 2, although many of his calculations were by necessity crude. Experimental studies reflecting indicator dilution principles include that of Crankshaw, Rosler and Ware,[32] who studied the relationship between peak arterial concentrations of thiopentone and duration of bolus injection.

ASSUMPTIONS AND LIMITATIONS OF THE MODEL

The present model is essentially a refinement of the approach of Crawford,[31] with the important addition of a detailed set of experimental data with which to validate the model. As the construction of any model requires making simple assumptions, these assumptions are examined. The most significant of these concerns the nature of the vascular mixing process (i.e. the relationship between drug injection and peak entering the lungs). Although the nature of this process has been described previously,[33] this type of analysis is relatively complex.[18] The approach used in the present model was essentially empirical and ignored intravascular transit time from the inferior vena cava to the pulmonary artery, which in the sheep was 4–9 s.[19] Fortunately, despite this, the predicted results closely matched those observed for a variety of injection rates and cardiac outputs. Note that the volume of the vascular mixing compartment is independent of the physicochemical properties of a drug, and that the injection site blood flow (Qinj) is not a determinant of the final concentration in the pulmonary artery.

The assumption of single-compartment, flow-limited kinetics in the lungs is also a simplification, as the lung probably behaves in a similar manner to a chromatographic column.[34] Again, any lag introduced by the passage of the peak from injection site to the lung was ignored in the final model (although accounted for in the curve-fitting process). The contribution of intravascular transit time of blood through the lung is likely to be small. The concept of an apparent first pass "retention" by the lung, whether a result of metabolism or an apparent extraction caused by "deep" distribution, is well supported by the literature,[10] particularly for basic drugs where the retention can be greater than 90%.

While more sophisticated models, such as dispersion models,[35] may be a more physiological description of myocardial drug kinetics, it seems likely that the essentially flow-limited nature of myocardial uptake of lignocaine[36] is retained in the present model.

The assumption that the target organ drug concentration is the sole determinant of the magnitude of target organ drug effects should also be made with caution, as this relationship does not hold if there is "tight" homeostatic control over the process affected by the drug (e.g. arterial pressure) or acute tolerance caused by receptor down regulation. For the lignocaine data, there is some suggestion of homeostatic control of myocardial contractility affecting the myocardial concentration–effect relationship as evidenced by the slight discrepancy between the model and data after 8 min in figure 6.

In general terms however, comparison of the model with these data (figs 3–6) suggests that addressing these assumptions would help "fine tune" the model, but that the assumptions are not sufficient to compromise the relevance of its quantitative and qualitative predictions.

IMPLICATIONS OF THE MODEL

While i.v. bolus administration of lignocaine is not common clinically, this drug was chosen because of the extensive published data set suitable for validating the model. However, it was felt that the general principles applicable to this drug and the heart would apply to any relatively lipophilic drug that acted in a well-perfused target organ.

CONTRIBUTION OF FIRST PASS DISTRIBUTION

Recirculation is often thought of as a rapid phenomenon, which is probably based on a knowledge of the behaviour of intravascular indicators. This study showed that recirculation of drugs takes considerably longer, and that the first passage through the heart can account for a large component of the myocardial concentrations and effects of lignocaine for the first 10 min after injection (the remainder is a result of recirculated drug entering the heart). This is consistent with the report of van Rossum and colleagues[37] that the mean transit time of many drugs in the body is of the order of 10 min. Note that the heart, which has a high relative perfusion, is often thought of as an organ in which recirculation occurs rapidly. It seems likely that the dominance of the first pass peak in initial organ concentrations is not a function of a failure of drug to recirculate, but rather indicates that the recirculated concentrations are much less than the first pass concentrations in this period.

SENSITIVITY ANALYSIS

While it has been noted previously that some pharmacokinetic parameters are related to cardiac output,[38] our work reinforces the fact that cardiac output is fundamental to the kinetics of bolus administration.[27,29] Indeed, it is more appropriate to consider bolus injection of a drug as an "indicator dilution" experiment "in reverse" rather than the traditional addition of a drug to a hypothetical volume. The concepts of the latter approach are difficult to reconcile with the actual physiological events. The role of myocardial blood flow was also highlighted by the model. This information provides greater insight into the effects of pathophysiological changes in blood flow distribution on dose requirements.

The model also provides insight into the effect of injection rate on initial drug concentrations and effects. An interesting feature of figure 9 is that the damping action of the lung and vascular mixing result in little difference in the time course of initial heart concentrations for injection rates between 1 and 60 s. If applicable to other drugs, this may indicate why in clinical practice the rate of bolus drug injection preferred by different clinicians is variable within this range. The model can also be used to test the relative merits of injection rate profiles other than a "square wave". We are currently pursuing this in our laboratory.

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Appendix

HYBRID PHYSIOLOGICAL MODELLING FOR PARAMETER ESTIMATION

This refers to the process whereby the parts of the system of interest are represented as a structural model, while the remainder is represented as empirical functions.[26,39] The complete model is validated by independently validating each of its component submodels in turn. Each submodel is treated as a hybrid of the complete model for which only its inputs and outputs are of interest. For example, for modelling myocardial kinetics the submodel was based on a modified single flow-limited compartment. The input functions were arterial concentrations and myocardial blood flow. These were fitted to empirical equations (a sum of exponentials for the blood concentrations and a fifth-order polynomial for the blood flow data). The structure and origin of the input function is irrelevant provided it provides an excellent fit for the input data. The output (coronary sinus concentrations) of the structural submodel was then curve-fitted to optimize its parameters by a least squares method based on the maximization the "model selection criteria (MSC)", which is essentially the Akaike information criterion scaled to normalize for data sets (Y) of different magnitudes (Micromath Scientific Software, Salt Lake City, UT, USA):

$$\mathrm{MSC}=\ln\left(\frac{\sum_{i=1}^{n} W_i(Y_{\mathrm{obs}_i}-\overline{Y_{\mathrm{obs}}})^2}{\sum_{i=1}^{n} W_i(Y_{\mathrm{obs}_i}-Y_{\mathrm{cal}_i})^2}\right)-\frac{2p}{n}$$

where w_i=a weighting term and p=number of parameters.

The input and output functions of each of the hybrid submodels discussed in the text are summarized in table 1a.

Table 1a Input and output functions of each of the hybrid submodels discussed in the text

Submodel	Input function(s)	Output function
Vascular mixing (eqns (2–5))	Dose rate	Pulmonary artery ICG concentrations
Lung kinetics (eqns (2–7))	Dose rate and pulmonary artery concentrations	Arterial concentrations
Myocardial kinetics (eqn (10))	Arterial concentrations myocardial blood flow	Coronary sinus concentrations
Myocardial dynamics (eqn (12))	Coronary sinus concentrations	Reductions in myocardial contractility

References

1. Horowitz JD, Powell AC. Myocardial uptake of drugs and clinical effects. *Clinical Pharmacokinetics* 1986; 11: 354–371.
2. Huang YF, Upton RN, Rutten AJ, Runciman WB. Intravenous bolus administration of subconvulsive doses of lignocaine to conscious sheep. Effect on circulatory function. *British Journal of Anaesthesia* 1992; 69: 368–374.
3. Horowitz JD, Dynon MK, Woodward E, Sia STB, McDonald PS, Morgan DJ, Goble AJ, Louis WJ. Short term myocardial uptake of lidocaine and mexiletine in patients with ischemic heart disease. *Circulation* 1986; 73: 987–996.
4. Huang YF, Upton RN, Runciman WB. Intravenous bolus administration of subconvulsive doses of lignocaine to conscious sheep. Relationships between myocardial pharmacokinetics and pharmacodynamics. *British Journal of Anaesthesia* 1993; 70: 556–561.
5. Gibaldi M, Perrier D. *Pharmacokinetics.* New York: Marcel Dekker, 1975.
6. Wood, M. Drug disposition and pharmacokinetics. In: Wood M, Wood AJJ, eds. *Drugs and Anesthesia, Pharmacology for Anesthesiologists,* 2nd Edn. Baltimore: Williams and Wilkins, 1990; 3–41.
7. Chiou WL. Potential pitfalls in the conventional pharmacokinetic studies: effects of initial mixing of drug in blood and the pulmonary first pass elimination. *Journal of Pharmacokinetics and Biopharmaceutics* 1979; 7: 527–536.
8. Chiou WL. Potential effect of early blood sampling schedule on calculated pharmacokinetic parameters of drugs after intravenous administration. *Journal of Pharmaceutical Sciences* 1980; 69: 867–868.
9. Henthorn TK, Avram MJ, Krejcie TC, Asada A, Kaczynski DA. Minimal compartmental model of indocyanine green. *American Journal of Physiology* 1992; **262**: H903–910.
10. Roerig DL, Kotrly KJ, Dawson CA, Ahlf SB, Gualtieri JF, Kampine JP. First-pass uptake of verapamil, diazepam, and thiopental in the human lung. *Anesthesia and Analgesia* 1989; 69: 461–466.
11. Runciman WB, Upton RN. Pharmacokinetics and pharmacodynamics—what is of value to anaesthetists? *Anaesthetic Pharmacology Review* 1994; 2: 280–293.
12. Lassen NA, Perl W. *Tracer Kinetic Methods in Medical Physiology.* New York: Raven Press, 1979.
13. Huang YF, Upton RN, Mather LE. The hemodynamic effects of intravenous bolus doses of meperidine in conscious sheep. *Anesthesia and Analgesia* 1994; 78: 442–449.
14. Huang YF, Upton RN, Runciman WB. Intravenous bolus administration of subconvulsive doses of lignocaine to conscious sheep. Myocardial pharmacokinetics. *British Journal of Anaesthesia* 1993; 70: 326–332.
15. Huang YF, Upton RN, Rutten A, Mather LE. The myocar-

dial pharmacokinetics of meperidine in conscious sheep. *Anesthesia and Analgesia* 1994; **79**: 987–994.

16. Chiba S. Comparative study of the action of antiarrhythmic drugs on sinoatrial nodal pacemaker activity and contractility in the isolated blood-perfused atrium of the dog. *Clinical and Experimental Pharmacology and Physiology* 1976; 3: 599–608.
17. Sheu SS. Cytosolic sodium concentration regulates contractility of cardiac muscle. *Basic Research in Cardiology* 1989; **84**: 35–45.
18. Beek WJ, Muttzal KMK. *Transport Phenomena.* London: Wiley, 1975.
19. Upton RN, Huang YF. The influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep. *British Journal of Anaesthesia* 1993; 70: 333–338.
20. Intaglietta M, Johnson PC. Principles of capillary exchange. In: Johnson PC, ed. *Peripheral Circulation.* New York: John Wiley and Sons, 1978; 141–166.
21. Holford NH, Sheiner LB. Kinetics of pharmacologic response. *Pharmacology and Therapeutics* 1982; **16**: 143–166.
22. Huang YF, Upton RN. An estimate of the rate of drug diffusion from the surface of heart and kidney—implications for representation as compartments. *Biopharmaceutics and Drug Disposition* 1993; **14**: 647–658.
23. Niazi S. Volume of distribution as a function of time. *Journal of Pharmacuetical Sciences* 1976; **65**: 452–454.
24. Henthorn TK, Avram MJ, Krejcie TC. Intravascular mixing and drug distribution: The concurrent disposition of thiopental and indocyanine green. *Clinical Pharmacology and Therapeutics* 1989; **45**: 56–65.
25. Krejcie TC, Henthorn TK, Shanks CA, Avram MJ. A recirculatory pharmacokinetic model describing the circulatory mixing, tissue distribution and elimination of antipyrine in the dog. *Journal of Pharmacology and Experimental Therapeutics* 1994; **269**: 609–616.
26. Wada DR, Ward DS. The hybrid model: a new pharmacokinetic model for computer-controlled infusion pumps. *IEEE Transactions on Biomedical Engineering* 1994; 41: 134–142.
27. Homer LD, Small A. A unified theory for estimation of cardiac output, volumes of distribution and renal clearances from indicator dilution curves. *Journal of Theoretical Biology* 1977; **64**: 535–550.
28. Cutler DJ. A linear recirculation model for drug disposition. *Journal of Pharmacokinetics and Biopharmaceutics* 1979; 7: 101–116.
29. Weiss M, Forster W. Pharmacokinetic model based on circulatory transport. *European Journal of Clinical Pharmacology* 1979; **16**: 287–293.
30. Weiss M. Modelling of initial distribution of drugs following intravenous bolus injection. *European Journal of Clinical Pharmacology* 1983; **24**: 121–126.
31. Crawford JS. Speculation: The significance of varying the mode of injection of a drug. With special reference to the brain and placenta. *British Journal of Anaesthesia* 1966; **38**: 628–640.
32. Crankshaw DP, Rosler A, Ware M. The short term distribution of thiopentone in the dog. *Anaesthesia and Intensive Care* 1979; 7: 148–151.
33. Guyton AC, Jones CE, Coleman TG. *Cardiac Output and its Regulation,* 2nd Edn. Philadelphia: WB Saunders Company, 1973.
34. Jones ME, Nicholas TE. The pharmacokinetics of the intravenous steroid anesthetic alphaxolone in the isolated perfused rat lung. *Journal of Pharmacokinetics and Biopharmaceutics* 1981; **9**: 343–355.
35. Roberts MS, Rowland MA. Dispersion model of hepatic elimination: 1. Formulation of the model and bolus considerations. *Journal of Pharmacokinetics and Biopharmaceutics* 1986; 14: 227–260.
36. Zito RA, Caride VJ, Holford T, Zaret BL. Regional myocardial kinetics of lidocaine in experimental infarction: Modulation by regional blood flow. *American Journal of Cardiology* 1981; 47: 265–270.
37. van Rossum JM, Burgers J, van Lingen G, de Bie J. Pharmacokinetics—a dynamic systems approach. *Trends in Pharmacological Sciences* 1983; January: 27–30.
38. Henthorn TK, Krejcie TC, Avram MJ. The relationship between alfentanil distribution kinetics and cardiac output. *Clinical Pharmacology and Therapeutics* 1992; 52: 190–196.
39. Gerlowski LE, Jain RK. Physiologically based pharmacokinetic modeling: Principles and applications. *Journal of Pharmaceutical Sciences* 1983; 72: 1103–1127.

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Measurement of cardiac output by transoesophageal Doppler echocardiography in anaesthetized horses: comparison with thermodilution

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Summary

In order to determine if transoesophageal Doppler echocardiography could be used to estimate cardiac output in anaesthetized horses, we have compared the technique with estimations of cardiac output by thermodilution in eight healthy adult thoroughbreds. Measurements of aortic blood flow velocity were made by high pulse repetition frequency (HPRF) and continuous wave (CW) Doppler echocardiography from a 3.5-MHz transoesophageal probe. Cardiac output was increased during the study by administration of dobutamine, providing a range of cardiac output measurements by thermodilution from 15.0 to 64.4 litre min^{-1}. Estimations derived from CW Doppler overestimated cardiac output compared with thermodilution (bias=4.0 litre min^{-1}). Estimations from HPRF Doppler echocardiography more closely reflected measurements obtained by thermodilution (bias=0.7 litre min^{-1}). Limits of agreement between the techniques were similar for both modes of insonation (HPRF=−7.7 to 9.1 litre min^{-1}, CW=−4.9 to 12.8 litre min^{-1}). There were significant differences in bias between both Doppler techniques and thermodilution for individual horses. As a result, for any individual horse, limits of agreement between the techniques were closer (HPRF=±6.4 litre min^{-1}, CW=±7.6 litre min^{-1}). We conclude that transoesophageal echocardiography provided an alternative, effective and non-invasive method for measurement of cardiac output in anaesthetized horses. (*Br. J. Anaesth.* 1996; **77**: 773–780)

Key words

Measurement techniques, cardiac output. Measurement techniques, thermodilution. Measurement techniques, transoesophageal echocardiography. Horse.

Halothane anaesthesia in horses produces cardiac depression and systemic hypotension.[1 2] These adverse cardiovascular effects have been implicated in the higher incidence of intraoperative morbidity[3 4] and mortality[5] in horses compared with other species. Cardiovascular monitoring during equine anaesthesia is restricted generally to recording heart rate, rhythm and arterial pressure.[6 7] Information on the mechanisms of cardiovascular dysfunction which occur during general anaesthesia in this species has been limited by the invasive nature of the monitoring techniques that were available previously. The availability of echocardiography has removed many of these limitations; the shift in frequency which occurs when ultrasound is reflected from a moving object can be used to calculate blood flow velocity. Doppler echocardiography measures blood velocity in targeted areas of the heart and great vessels. Integration of the resultant velocity–time curve gives a value which represents the summated distance travelled by the blood with each cardiac cycle. If this value is multiplied by the cross-sectional area of the vessel and heart rate, an estimate of cardiac output is obtained.[8]

Cardiac output in horses is measured most frequently by thermodilution or dye dilution techniques,[9–12] although the need for cardiac catheterization and the associated risks tend to limit the procedure to research applications. Recent studies have shown that transoesophageal echocardiography is feasible in anaesthetized horses and that the technique provides parallel alignment between ultrasound beam and aortic blood flow,[13] a necessary criterion for accurate estimations of velocity by Doppler echocardiography. In this study we aimed to assess correlation and agreement between transoesophageal Doppler assessment of aortic flow and cardiac output determined by thermodilution in horses during halothane anaesthesia. Aortic flow velocity–time curves were obtained by both pulsed and continuous

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wave methods of insonation and limits of agreement of both techniques were compared.

Materials and methods

EXPERIMENTAL PREPARATION

The study conformed to the UK Animals Act (Scientific Procedures, 1986, Home Office licence No. PPL 60/1674). We studied eight thoroughbred horses (four mares and four geldings), aged 3–6 yr and weighing 490–600 kg (mean 545 kg). The horses were clinically normal, housed indoors and kept in moderate work. Food, but not water, was withheld from the horses from 20:00 on the day preceding the study. On the morning of the procedure, the skin overlying the left jugular vein was anaesthetized by surface application of EMLA cream (Astra, Kings Langley, UK) followed 40 min later by subcutaneous administration of 2% lignocaine. A 13-gauge over-the-needle catheter (Intaflon, Vygon, Cirencester, UK) was placed in the jugular vein through the desensitized skin.

In a padded induction area, the α_2 adrenoreceptor agonist, romifidine 100 μg kg^{-1} (Sedivet, Boehringer Ingelheim, Bracknell, UK) was administered i.v. via the jugular catheter. Anaesthesia was induced 5 min later with ketamine 2.2 mg kg^{-1} i.v. The trachea was intubated with a 25- or 30-mm cuffed tracheal tube which was adapted to allow collection of gas from its distal end.[14] Initially the horses breathed spontaneously from a large animal circle system supplied with halothane in 100% oxygen. When an adequate depth of anaesthesia was obtained the horse was transferred to a padded operating table and ventilation was controlled using intermittent positive pressure (Large Animal Anaesthesia Control Centre, North American Drager, Telford, PA, USA). Initially, ventilatory frequency and tidal volume were set to 10 bpm and 7 litre, respectively. A commercial blood-gas analyser was used to monitor arterial Pa_{CO_2} from arterial blood samples obtained from the great metatarsal artery. Minor adjustments of the ventilator controls were used to maintain Pa_{CO_2} at 4.6–6.0 kPa. End-tidal halothane concentration was measured from end-expired gas sampled from the end of the tracheal tube using a calibrated anaesthetic gas monitor (Servo Gas monitor 120, Siemens PLC, Cumbernauld, UK). The vaporizer was adjusted throughout the study to maintain an end-tidal concentration of 0.9%.

INSTRUMENTATION

Echocardiography

Immediately after induction of anaesthesia a 3.5-MHZ transoesophageal echocardiographic probe (Vingmed Sound, Horten Norway) was inserted into the oesophagus via the ventral nasal meatus. The probe was purpose-made for equine use and was constructed from a 160-cm human colonoscope.[13] The probe was used in conjunction with a Vingmed CFM 700 echocardiograph. The maximum depth for 2-dimensional (2-D) and M-mode imaging was 24 cm. The frame update rate was 19–55 frames per second, depending on the sector angle selected and the imaging depth. The maximum depth for colour flow mapping and spectral Doppler studies was 20 cm. Doppler studies were conducted using the transducer in high pulse repetition frequency (HPRF) and continuous wave (CW) mode, with ultrasound emitted at a frequency of 2.5 MHz.

The probe was advanced into the oesophagus through the external nares until a long axis view of the left ventricular outflow tract and aorta were obtained by 2-D echocardiography.[13] The HPRF Doppler sample volume was then guided to the centre of the vessel above the aortic valve in the area where colour flow Doppler echocardiography demonstrated the fastest flowing blood.[15] Continuous wave ultrasound was directed in the same axial position down the whole length of the aorta and left ventricular outflow tract. When the sample volume had been positioned the transducer was dedicated to acquisition of Doppler data. Adequate alignment with aortic blood flow was assumed from the clarity of the audible signal and when a complete velocity envelope was obtained.[16]

Thermodilution

After the horses had been positioned in left lateral recumbency on a padded operating table, two 8-F percutaneous catheter introducer sets (Haemaquet-Steri Lock, Bard Ltd, Crawley, UK) were inserted into the right jugular vein, using a percutaneous Seldinger technique. A 150-cm long thermodilution catheter (od=2.31 mm) (Columbus Instruments, Columbus, OH, USA) was inserted via one introducer until pressure recordings from its distal port indicated that it was situated in the pulmonary artery.

The thermodilution catheter had a proximal port, but high internal resistance to injectate flow precluded its use for thermal indicator administration during thermodilution studies. A separate catheter was made from a 200-cm length of polyethylene tubing (800/200/225 (od=1.6 mm), Portex Arterial Medical, South Gate, London, UK) for delivery of the thermal indicator. The atrial end of the catheter was sealed closed by heat from a Bunsen burner. Five holes (diameter=0.5 mm) were pierced along the final 4 cm of catheter body, using a hot 14-gauge i.v. needle. The open end of the tubing was then placed over the body of a 14-gauge i.v. needle, the hub of which was connected to a pressure injector. The pressure injector was driven by compressed air at an operating pressure of 30 pounds per square inch (psi) which ensured that the charge of 45 ml of injectate was delivered within 3 s, as recommended by Ganz and Swan.[17] A test injection of 45 ml of 0.9% saline solution was then made via the catheter using the pressure injector to ensure that flow occurred evenly through the side holes and that injection was completed within 3 s. The catheter was sterilized using ethylene oxide.

The sterile catheter was pre-filled with heparinized saline (5 u. ml^{-1}) and introduced into the right atrium by advancing it down the second percutaneous introducer set. To position the catheter it was connected to a pressure transducer, and advanced down the introducer until a characteristic right ventricular pressure waveform was obtained. It was then withdrawn until the pressure trace indicated it had just re-entered the right atrium. With the catheter in position a test injection with 45 ml of 0.9% saline was carried out while observing a 2-D image of the right atrium obtained by transthoracic echocardiography. Correct catheter placement was confirmed by the sudden short-lived appearance of multiple echogenic speckles in the right atrium, coinciding with injection.

A Cardiomax II model 85 cardiac output computer (Columbus Instruments, Columbus, OH, USA) was used to measure cardiac output by thermodilution. Previous work had demonstrated that satisfactory dilution curves could be obtained from standing horses when 45 ml of saline at room temperature were injected using a pressure injector through the separate catheter in the right atrium.[18] Normal saline stored at room temperature was used as the thermal indicator for all horses. During these studies, ambient temperature varied between 14.4 and 19.2 °C. The dilution curves from each estimation were displayed on a chart recorder allowing visual inspection of each curve. Only measurements from dilution curves with a characteristic fast attack slope and a slower return to baseline were acceptable.

DATA COLLECTION

Data from HPRF and CW transoesophageal echocardiographic studies were measured by a single observer from video-taped images of aortic blood flow velocity spectra. Cardiac output was calculated from aortic velocity spectra using the equation:

$$\text{cardiac output} = \text{VTI} \times \text{aortic cross-sectional area} \times \text{heart rate}$$

where VTI=area under the velocity spectra (velocity time integral).

Area under individual velocity envelopes (VTI) was measured using software within the echocardiograph. The modal velocity delineated by the brightest line in the velocity envelope was used to delineate the area beneath spectra derived from HPRF studies, while maximum velocity was used for CW envelopes. Doppler signals from five consecutive cardiac cycles were measured for each cardiac output estimation and mean VTI and heart rate for the group of five cycles were calculated. Heart rate was calculated from the five corresponding RR intervals from the electrocardiogram of the ultrasonograph.

The cross-sectional area of the aorta was calculated from the aortic diameter measured from a 2-D long axis image of the aorta at the level of the sino-tubular junction.[14] In this view, the anatomical boundaries of the vessel are parallel to the ultrasound beam, resulting in considerable lateral broadening of the vessel walls.[19] According to the recommendations of Hatle and Angelsen[16] vessel diameter was measured perpendicular to the long axis of the aorta by a line joining the middle of the band of echoes corresponding to the vessel walls. To obtain each diameter, three measurements were made during systole from three consecutive cardiac cycles and an average value obtained. The 2-D images needed for measurements were recorded on video tape immediately before each set of cardiac output measurements.

Mechanical ventilation was discontinued before each cardiac output measurement, and the ventilator was switched off in the expiratory pause just after an inspiratory cycle was complete. Injection of thermal contrast was initiated by pressing the pressure injector foot pedal, to coincide with the second "p" wave of the ECG after the ventilator was stopped. The record facility of the VHS video recorder on the Vingmed CFM 700 was also activated.

Each estimate of cardiac output by Doppler echocardiography was compared with a mean of three closely successive thermodilution estimates. In accordance with the manufacturer's instructions, at least 60 s were allowed to elapse between consecutive thermodilution measurements. The first of the three injections coincided with video recording of aortic velocity waveforms by HPRF Doppler echocardiography. The insonation mode of the Doppler echocardiograph was then changed from HPRF to CW between the first and second thermodilution estimations. Doppler spectra were not recorded coincident with the final thermodilution measurement in the sequence.

EXPERIMENTAL PROCEDURE

A group of five sets of three thermodilution measurements with associated Doppler recordings constituted a set of data for each horse at each cardiac output level. After the first group of five measurements were made, dobutamine 2 μg kg^{-1} min^{-1} was infused via the jugular catheter. After 15 min cardiac output estimations were repeated. The infusion rate was then increased to 4 μg kg^{-1} min^{-1}, and after another 15 min, the final set of cardiac output data were collected. At the start of each data acquisition period, 2-D images were recorded for measurement of aortic diameter. If the dobutamine infusion produced any disturbance to cardiac rhythm that was considered to be a risk to the horse, the infusion was discontinued and the procedure was terminated.

STATISTICAL ANALYSIS

Agreement between the two techniques was assessed using the methods of Altman and Bland.[20] The mean difference between cardiac output estimations made by Doppler techniques and thermodilution (defined as bias) was determined for all pairs of measurements (ΔCO_p). The SD of these differences ($\text{SD}\Delta CO_p$) was then used to determine limits of agreement for the pooled data (defined as bias $\pm 2\text{SD}\Delta CO_p$). The analysis of Altman and Bland[20] is designed for single pairs of measurements originating from independent subjects. As in many previous studies, in this study multiple measurements of cardiac output were made in a small number of individuals. To further distinguish within-subject and between-subject variation in bias and limits of agreement, the following additional analysis was performed: differences in bias between horses were assessed using one-way analysis of variance. The mean difference between techniques and the variance of the differences were determined for each horse. A within-subject SD of the difference was determined from the mean of the variances from individual horses (SDΔCO_w). The limits of agreement between techniques for an individual were then determined ($\pm$2SDΔCO_w). Measurements of aortic diameter before and during dobutamine infusion were compared by paired Student's *t* test. Although it is recognized that calculation of product moment correlation coefficient (*r*) is not an appropriate method to assess agreement between measurement techniques,[21] the linear relationships between the HPRF and CW derived cardiac output estimates and those from thermodilution were determined. The analysis was performed to allow comparison of our data with similar studies in other species in which calculation of *r* was the sole method of data analysis.

Results

A total of 95 comparisons of cardiac output estimations from Doppler and thermodilution techniques were made for both insonation modes. Only five estimates were obtained from one horse, as supraventricular tachycardia (heart rate 186 beat min^{-1}) commenced 10 min after infusion of dobutamine 2 $\mu g\ kg^{-1}\ min^{-1}$. Supraventricular tachycardia (heart rate >150 beat min^{-1}) occurred in three more horses during infusion of dobutamine 4 $\mu g\ kg^{-1}\ min^{-1}$ before cardiac output estimations had been made.

The range of cardiac output values measured by thermodilution during the study was 14.1–65.4 litre min^{-1} with a mean value of 26.7 litre min^{-1}. When agreement between the two methods was assessed for the pooled data, estimates by CW Doppler echocardiography tended to overestimate those by thermodilution on average (bias) by 4.0 litre min^{-1} (fig. 1). Estimates derived from HPRF spectra agreed more closely with the invasive method, showing a positive bias of only 0.7 litre min^{-1} (fig. 2). The SD of the differences between Doppler-derived estimates and thermodilution (SDΔCO_p) was slightly less for HPRF estimates (4.2 litre min^{-1}) than for those derived from CW (4.4 litre min^{-1}). As a result the limits of agreement (bias$\pm$2SDΔCO_p) were slightly narrower for HPRF derived estimates (−7.7 to 9.1 litre min^{-1}) than for CW estimates (−4.9 to 12.8 litre min^{-1}). These limits of agreement represented −34% to 28% of mean cardiac output

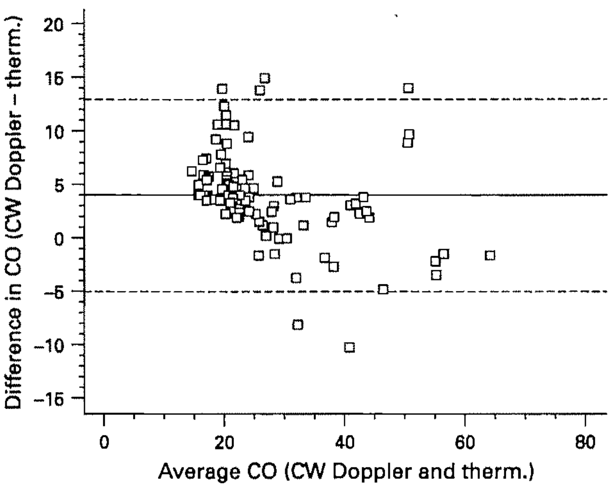

Figure 1 Differences in cardiac output (CO) measured by CW Doppler echocardiography and the mean of three consecutive thermodilution (therm.) measurements *vs* the average of the two techniques. CO is measured in litre min^{-1}.The bias, 4.0 litre min^{-1}, is indicated by the solid line and the upper and lower limits of agreement, −4.9 to 12.8 litre min^{-1}, by the broken lines.

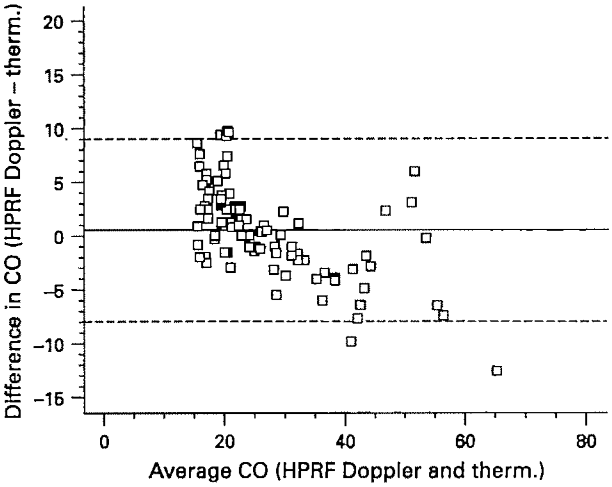

Figure 2 Differences in cardiac output (CO) measured by HPRF Doppler echocardiography and the average of three consecutive thermodilution (therm.) measurements *vs* mean of the two techniques. CO is measured in litre min^{-1}. The bias, 0.7 litre min^{-1}, is indicated by the solid line and the upper and lower limits of agreement, −7.7 to 9.1 litre min^{-1}, by the broken lines.

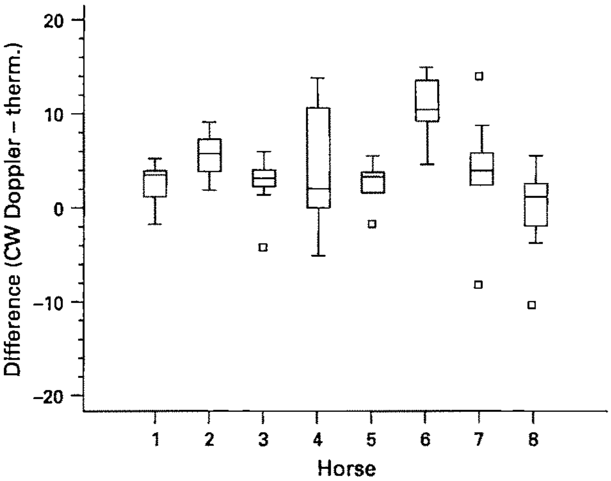

Figure 3 Box and whisker plot of differences in cardiac output (CO) measured by CW Doppler echocardiography and the average of three consecutive thermodilution (therm.) measurements in each of eight anaesthetized horses. Differences in CO are measured in litre min^{-1}. The horizontal dividing line in each box is the median value, the upper and lower border of each box are the upper and lower quartiles. Maximum and minimum values within one interquartile range are depicted by the vertical whiskers. Outlying data are shown by points. Number of measurements per horse: horse 1=15; horse 2=15; horse 3=15; horse 4=10; horse 5=10; horse 6=5; horse 7=10; horse 8=15.

Table 1 Median (range) values for aortic diameter, measured from 2-D echocardiography. Paired Student's *t* test revealed no significant difference in vessel diameters during the infusion periods (P=0.95). Mean difference from control=difference between diameters at each infusion rate of dobutamine and control value

	Control 0.9% halothane	Dobutamine 2 $\mu g\ kg^{-1}$	Dobutamine 4 $\mu g\ kg^{-1}\ min^{-1}$
No. of horses	8	7	5
Aortic diameter (cm)	7.10 (6.53–7.58)	7.07 (6.48–7.50)	7.16 (6.48–7.65)
Difference from control (cm)		−0.01 (−0.14 to 0.12)	0.07 (−0.30 to 0.4)

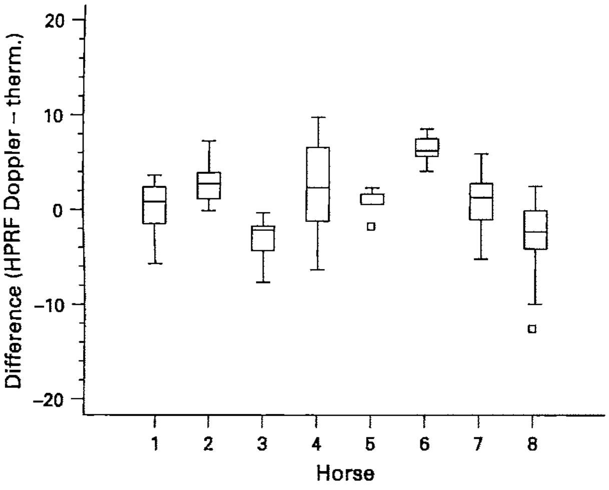

Figure 4 Box and whisker plot of differences in cardiac output (CO) measured by HPRF Doppler echocardiography and the average of three consecutive thermodilution (therm.) measurements in each of eight anaesthetized horses. Differences in CO are measured in litre min^{-1}. The horizontal dividing line in each box is the median value, the upper and lower border of each box are the upper and lower quartiles. Maximum and minimum values within one interquartile rangs are depicted by the vertical whiskers. Outlying data are shown by points. Number of measurements per horse: horse 1=15; horse 2=15; horse 3=15; horse 4=10; horse 5=10; horse 6=5; horse 7=10; horse 8=15.

for HPRF estimates and −18% to 48% for CW estimates. The product moment correlation coefficients for the two methods of insonation were 0.92 (CW) and 0.93 (HPRF).

The calculated bias between estimates from both insonation modes and thermodilution differed significantly between horses (P<0.0001) (figs 3, 4). When mean bias was calculated as the average of values calculated for each individual horse, bias for CW estimates was 4.4 litre min^{-1} and that for HPRF, 1.3 litre min^{-1}. The SD of bias between horses were 3.0 litre min^{-1} (HPRF) and 3.1 litre min^{-1} (CW). The limits of agreement between techniques for an individual horse were ±6.4 litre min^{-1} (HPRF) and ±7.6 litre min^{-1} (CW), representing ±23% and ±28% of mean cardiac output, respectively.

There were no significant changes of clinical importance in aortic diameter with any infusion rate of dobutamine(table 1).

Discussion

Estimations of cardiac output by transoesophageal Doppler echocardiography showed a close linear relationship with measurements obtained by thermodilution. In addition, the limits of agreement between the two techniques, expressed as a percentage of mean cardiac output, were narrower in this study than those determined for humans. In human studies, blood flow across the mitral and pulmonary valves, not the aortic valves, was used most commonly to obtain velocity spectra for measurement of VTI.[22-26] Mitral and pulmonary blood flows were chosen because of superior alignment with the ultrasound beam from an oesophageal transducer in humans. The poor correlations (0.65–0.80) and wider limits of agreement obtained in these studies probably reflect difficulties in measurement of mitral and pulmonary valve areas.[27] In biped species the descending aorta runs parallel to the oesophagus, therefore it is difficult to align aortic blood flow and ultrasound from an oesophageal transducer. One group of workers compared cardiac output calculations from human aortic blood flow profiles obtained by transoesophageal echocardiography with measurements by thermodilution.[28] Because of the wide angle of incidence between the beam and the descending aorta, the device was calibrated by calculating a constant from a second transcutaneous Doppler transducer placed in the suprasternal notch. Using this technique these workers obtained a correlation of 0.91 between the two techniques and limits of agreement within 26% of mean cardiac output. Recently, a similar study failed to reproduce these results, obtaining limits of agreement between the two techniques of −44% to +36% of mean cardiac output by thermodilution.[29] Because of poor agreement between methods, the authors concluded that the technique could not replace estimation of cardiac output by the thermodilution method. Difficulty in aligning with aortic blood flow and poor results when pulmonary or mitral blood flow is used have ensured that transoesophageal Doppler echocardiography is not used widely for monitoring cardiac output in anaesthetized humans.

In horses and other quadrupeds, the anatomical relationship of aorta and oesophagus differs from humans, and a transducer within the oesophagus can be aligned with blood flow in the ascending aorta. This probably explains why the agreement and linear relationships obtained by transoesophageal techniques in horses are better than those reported in human studies. The correlations obtained in the equine transoesophageal studies were similar to those obtained in many human studies using transthoracic echocardiography.[30-33] Cardiac output estimations using transthoracic Doppler echocardiography are now used widely in human medicine,[8] and it is generally accepted that estimates derived from Doppler echocardiography agree as well with the standard methods (Fick principle, thermal and dye dilution) as the standard methods agree with each other.[34]

Similar studies have been performed in standing horses when cardiac output estimations from aortic velocity spectra derived by transthoracic echocardiography were compared with measurements made by thermodilution.[18] Overall the linear relationship and limits of agreement of the two techniques were consistently worse from the transthoracic studies in standing horses than was found in our transoesophageal study in anaesthetized horses. Poor alignment with aortic blood flow would consistently underestimate volumetric flow, but have little effect on the limits of agreement. In previous transthoracic studies in standing horses the narrowest limits of agreement were -12.9 to 11.8 litre min^{-1},[35] compared with -7.7 to 9.1 litre min^{-1} in this study. As the technique of vessel area measurement was similar in both methods, the narrower limits of agreement in the transoesophageal study must reflect more consistent alignment with blood flow in individual horses. The reference long axis 2-D image obtained from transoesophageal echocardiography that was used to guide placement of the Doppler sample volume was repeatable in every horse and the image did not appear to vary between individuals.[13] Marked inter-subject variation in correlation between transthoracic Doppler measurements of cardiac output and those from the thermodilution and Fick methods has been reported previously in humans.[36] Analysis of inter-subject variation in this study revealed significant differences in bias and limits of agreement in individual horses. This variability of bias could result from altered alignment between ultrasound beam and aortic flow, or from inaccurate vessel area measurement in individual subjects. In a study in humans,[36] this inter-subject variability remained after flow area was removed from the calculation of cardiac output, corroborating the findings of other workers that there was marked variation in alignment between ultrasound beam and aorta in individual patients during transthoracic echocardiography.[37 38] The within-subject variation caused by the requirement to realign the ultrasound transducer with blood flow for each repeated measurement in an individual during transthoracic echocardiography should also be minimized in transoesophageal echocardiography, as once in position, the transducer remains fixed in the oesophagus. Unfortunately other workers have not analysed within-subject variation in bias and limits of agreement in previous comparison studies, and therefore it is not possible to compare the equine data with other species. However, data from this study indicated the important effects of patient variation on bias and agreement between techniques, a situation which is likely to occur in humans in addition to horses.

It is generally accepted that inaccuracy in the determination of flow area is the major source of error in the Doppler technique.[31 39] Because of difficulties in its accurate measurement, it has been suggested by some workers that velocity time integral (VTI) alone can be used to reflect changes in stroke volume,[39] as a strong relationship has been demonstrated between the two variables.[33 38] The product of VTI and heart rate (minute distance) has also been proposed as an accurate and repeatable indicator of cardiac output.[40 41] McLennan and coworkers[41] showed that *in vitro* the method detected changes in flow rate of 33% with 95% certainty, a sensitivity which is similar to that of the thermodilution technique *in vitro* under conditions of pulsatile flow. In our studies, no significant measurable differences in aortic diameter were found at different cardiac output levels so that omission of vessel area from flow calculations in anaesthetized horses may be worthy of consideration. It is possible that failure to detect changes in diameter may reflect the poor sensitivity of the 2-D ultrasound measurement method, rather than indicating that aortic area is unaffected by stroke volume. Omission of vessel area measurement would also remove another source of inter-subject variation. Use of standard area measurements similar to the normograms used for aortic diameter derivation in human studies[42] may have further narrowed the limits of agreement determined for the pooled data in this study.

Continuous wave Doppler echocardiography has been used for computation of aortic flow in humans, using both transthoracic[32 33] and transoesophageal techniques.[23 28] Most of the early studies reported in the medical literature were performed using CW insonation as accuracy of range gated (HPRF) Doppler was poor until the advent of fast Fourier transform analysis.[32] In humans, the size of the HPRF ultrasound transducer limited access to the suprasternal window, the echocardiographic view providing most consistent and accurate alignment with aortic blood flow. This practical difficulty also encouraged use of the CW method. In the CW technique, maximum velocity is used to delineate the bounds of the flow velocity envelope for calculation of the velocity time integral. The spectra produced from CW studies are complex as they are formed from velocity information from along the depth of the beam. It is therefore possible that maximum velocity comes from a site other than in the aorta. Theoretically, maximum velocity should occur at the narrowest point in the circulation, which for the aorta and left ventricular outflow tract should be the aortic valve annulus. It has been shown that maximum velocity is less sensitive to poor angulation than the modal velocity, used in the HPRF studies,[43] and this may explain why some authors found better agreement between Doppler and thermodilution when CW rather than HPRF insonation was used.[44] In this study the magnitude of the bias was increased when spectra were derived using CW Doppler echocardiography. As maximum, rather than median, velocity is used to obtain VTI this is not surprising. However, the limits of agreement between Doppler and thermodilution measurements were also slightly wider when the CW mode of insonation was used. The reason for this is unclear, as use of the maximum velocity should produce a positive bias, but have no effect on the agreement between the two techniques. As the transoesophageal echocardiography probe was not moved between recording alternate HPRF and CW velocity spectra, the wider limits of agreement cannot be attributed to altered alignment. It is possible that in some individuals the CW technique detected a maximum velocity that came from the left ventricular outflow tract or from accelerated flow around the aortic arch providing a further source of between-subject variation.

In conclusion, we have demonstrated that transoesophageal Doppler echocardiography provided a useful alternative to thermodilution for measurement of cardiac output in anaesthetized horses. This infers that transoesophageal echocardiography may provide an alternative method of cardiac output estimation in other smaller quadruped species in whom cardiac catheterization and instrumentation is difficult or inappropriate.

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References

1. Gillespie JR, Tyler WS, Hall LW. Cardiopulmonary dysfunction in anesthetised, laterally recumbent horses. *American Journal of Veterinary Research* 1969; **30**: 61–72.
2. Eberly VE, Gillespie JR, Tyler WS, Fowler ME. Cardiovascular values in the horse during halothane anesthesia. *American Journal of Veterinary Research* 1968; **29**: 305–314.
3. Lindsay WA, Robinson GM, Brunson GM, Majors LJ. Induction of equine postanesthetic myositis after halothane-induced hypotension. *American Journal of Veterinary Research* 1989; **50**: 404–410.
4. Grandy JL, Steffey EP, Hodgson DS, Woliner MJ. Arterial hypotension and the development of postoperative myopathy in halothane anesthetised horses. *American Journal of Veterinary Research* 1987; **48**: 192–197.
5. Johnston GM, Taylor PM, Holmes MA, Wood JLN. Confidential enquiry of perioperative fatalities: Preliminary results. *Equine Veterinary Journal* 1995; **27**: 193–201.
6. Hubbel JAE. Monitoring. In: Muir WW, Hubbel JAE, eds. *Equine Anesthesia: Monitoring and Emergency Therapy*. St Louis: Mosby Year Book, 1991; 153–180.
7. Lumb WV, Wynn-Jones E. Monitoring anaesthesia. In: Lumb WV, Wynn-Jones E, eds. *Veterinary Anaesthesia*. Philadelphia: Lea & Febiger, 1985; 493–520.
8. Haites NE, McLennan FM, Mowat DHR, Rawles JM. How far is the cardiac output. *Lancet* 1984; **ii**: 1025–1027.
9. Dunlop CI, Hodgson DS, Chapman PL. Thermal dilution estimation of cardiac output at high flows. *FASEB Journal* 1992; **2**: A1287.
10. Muir WW, Skarda RT, Milne DW. Estimation of cardiac output in the horse by thermodilution techniques. *American Journal of Veterinary Research* 1976; **37**: 697–700.
11. Hillidge CJ, Lees P. Cardiac output in the conscious and anaesthetised horse. *Equine Veterinary Journal* 1975; **7**: 16–20.
12. Fisher EW, Dalton RG. Cardiac output in horses. *Nature (London)* 1959; **184**: 2020–2021.
13. Young LE, Blissitt KJ, Clutton RE, Molony V, Darke PGG. Feasibility of transoesophageal echocardiography for evaluation of left ventricular performance in anaesthetised horses. *Equine Veterinary Journal* 1995; **19** (Suppl.): 63–70.
14. Young LE. Measurement of Left Ventricular Function in Anaesthetised Horses Using Transoesophageal Echocardiography, PhD Thesis. Edinburgh: University of Edinburgh, 1995; 1–282.
15. Blissitt KJ, Bonagura JD. Pulsed wave Doppler echocardiography in normal horses. *Equine Veterinary Journal* 1995; **19** (Suppl): 38–46.
16. Hatle LK, Angelsen B. Flow computation. In: Hatle LK, Angelsen B, eds. *Doppler Echocardiography*. Philadelphia: Lea and Febiger, 1985; 153–184.
17. Ganz W, Swan HJC. Measurement of blood flow by thermodilution. *American Journal of Cardiology* 1972; **29**: 241–246.
18. Long KJ, Young LE, Jones RS, Darke PGG, Utting JE. Determination of cardiac output in the standing horse by thermodilution and Doppler echocardiography. *British Journal of Anaesthesia* 1992; **68**: 447P.
19. Feigenbaum H. *Echocardiography*, 5th Edn. Philadelphia: Lea & Febiger, 1993.
20. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician* 1983; **32**: 307–313.
21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**: 307–310.
22. Ryan T, Page R, Bouchier-Hayes D, Cunningham AJ. Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: Comparison with the thermodilution technique. *British Journal of Anaesthesia* 1992; **69**: 101–104.
23. Gorcsan J, Diana P, Ball BA, Hattler BG. Intraoperative determination of cardiac output by transesophageal continuous wave Doppler. *American Heart Journal* 1992; **123**: 171–176.
24. Muhiudeen IA, Kuecherer HF, Lee E, Cahalan MK, Schiller NB. Intraoperative estimation of cardiac output by transesophageal pulsed Doppler echocardiography. *Anesthesiology* 1991; **74**: 9–14.
25. LaMantia KR, Carter J, Davis E, Ezekowitz M. Measurement of cardiac output by transesophageal pulsed wave doppler: Comparison of two techniques. *Anesthesia and Analgesia* 1990; **70**: S450.
26. Ellis JE, Runyon-Hass A, Lichtor JL, Roizen MF. Can Doppler ultrasound, targeted by two dimensional transesophageal echocardiography, be used to measure cardiac output? *Anesthesiology* 1967; **67**: A638.
27. Sahn DJ. Determination of cardiac output by echocardiographic Doppler methods: Relative accuracy of various sites for measurement. *Journal of the American College of Cardiologists* 1985; **6**: 663–665.
28. Perrino AC, Fleming J, LaMantia KR. Transesophageal Doppler ultrasound: Evidence for improved cardiac output monitoring. *Anesthesia and Analgesia* 1990; **71**: 651–657.
29. Keyl C, Rodig G, Lemberger P, Hobbhahn J. A comparison of the use of transoesophageal Doppler and thermodilution techniques for cardiac output determination. *European Journal of Anaesthesiology* 1996; **13**: 136–142.
30. Dubin J, Wallerson DC, Cody RJ, Devereux RB. Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determination. *American Heart Journal* 1990; **120**: 116–123.
31. Ihlen H, Amlie JP, Dale J, Forfang K, Nitter-Haige S, Simonsen S, Myhre E. Determination of cardiac output by Doppler echocardiography. *British Heart Journal* 1984; **51**: 54–60.
32. Nishimura L. Noninvasive assessment of cardiac output by continuous wave Doppler echocardiography: Initial experience. *Mayo Clinic Proceeedings* 1984; **59**: 484–489.
33. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS. Non invasive Doppler determination of cardiac output in man; clinical validation. *Circulation* 1983; **67**: 593–604.
34. Schuster AH, Nanda NC. Doppler echocardiographic measurement of cardiac output: Comparison with a non-golden standard. *American Journal of Cardiology* 1984; **53**: 257–259.
35. Long KJ. Echocardiographic studies of valvular and ventricular function in horses, PhD thesis. Edinburgh: University of Edinburgh, 1993; 221–238.
36. Christie J, Sheldahl LM, Tristani FE, Sagar KB, Ptacin MJ, Wann S. Determination of stroke volume during exercise: Comparison of two-dimensional and Doppler echocardiography. *Circulation* 1987; **76**: 539–547.
37. Angelsen BA, Brubakk AO. Transcutaneous measurement of blood flow velocity in the human aorta. *Cardiovascular Research* 1976; **10**: 368–379.

38. Sequeira RF, Light LH, Cross G, Raftery EB. Transcutaneous aortovelography. A quantitative evaluation. *British Heart Journal* 1976; 38: 443–450.
39. Haites NE, McLennan FM, Mowat DHR, Rawles JM. Assessment of cardiac output by the Doppler ultrasound technique alone. *British Heart Journal* 1985; 53: 123–129.
40. Moulinier L, Venet T, Schiller NB, Kurtz TW, Morris RC, Sebastian A. Measurement of aortic blood flow by Doppler echocardiography: Day to day variability in normal subjects and applicability in clinical research. *Journal of the American College of Cardiologists* 1991; 17: 1326–1333.
41. McLennan FM, Haites NE, Mackenzie JD, Daniel MK, Rawles JM. Reproducibility of linear cardiac output measurement by Doppler ultrasound alone. *British Heart Journal* 1986; 55: 25–31.
42. Perrino AC jr, Fleming J, LaMantia KR. Transesophageal Doppler cardiac output monitoring: Performance during aortic reconstructive surgery. *Anesthesia and Analgesia* 1991; 73: 705–710.
43. Brubakk AO, Givold SE. Pulsed Doppler ultrasound for measuring blood flow in the human aorta. In: Hatle L, Angelsen B, eds. *Doppler Ultrasound in Cardiology*. Philadelphia: Lea & Febiger, 1985; 185–193.
44. Fenger CK, Bertone JJ, Bonagura JD. Cardiac output in foals: Comparison of Doppler echocardiography and thermodilution measurement techniques. *Proceedings of the 9th ACVIM Forum.* Blacksburg, VA, USA: American College of Veterinary Internal Medicine, 1991: 872.

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Effect of halothane, isoflurane and desflurane on lower oesophageal sphincter tone

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Summary

We have studied the effects of volatile anaesthetics on lower oesophageal sphincter (LOS) tone in three groups of eight pigs allocated randomly to receive end-tidal concentrations of 0.5, 1.0 and 1.5 MAC of desflurane, isoflurane or halothane for 15 min. LOS and oesophageal barrier pressures (BrP = LOSP − gastric pressure) were measured using a manometric method. The decrease in BrP paralleled the decrease in LOS pressure and was significant at 0.5 MAC for isoflurane and at 1.0 MAC for halothane. At 1.5 MAC, BrP values were approximately 62% of baseline values for halothane, 37% for isoflurane and 83% for desflurane. Inter-group comparisons showed that BrP did not differ at baseline and at 0.5 MAC. At 1.0 MAC the effect of isoflurane on BrP was significantly different from desflurane ($P < 0.001$) and halothane ($P < 0.02$) whereas the effect of desflurane on BrP was not significantly different from halothane. At 1.5 MAC the effect of isoflurane on BrP was significantly different from desflurane ($P < 0.01$) and halothane ($P < 0.05$) whereas the effect of desflurane on BrP was not significantly different from halothane. We conclude that desflurane maintained BrP and this may be clinically important in patients at high risk of regurgitation. (*Br. J. Anaesth.* 1996; **77**: 781–783)

Key words
Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Anaesthetics volatile, desflurane. Gastrointestinal tract, lower oesophageal sphincter. Pig.

Induction and maintenance of anaesthesia can be achieved in patients breathing spontaneously by administration of volatile anaesthetic agents. Halothane is used widely in children for induction of anaesthesia via a face mask[1] (a situation with a high risk of pulmonary aspiration[2]). Halothane, isoflurane and desflurane are used for maintenance of anaesthesia.[3] The lower oesophageal sphincter (LOS) can be altered by anaesthetics. It has been reported previously that thiopentone,[4] opioids, neuromuscular blocking agents and benzodiazepines[5] affect the competency of the LOS. During anaesthesia it is important to be aware of these effects because a decrease in LOS tone is associated with an increased risk of regurgitation.[6 7] Therefore, it is clinically relevant to evaluate the effects of these anaesthetics on LOS tone. Anaesthetics which decrease lower oesophageal pressure (LOSP) decrease the efficacy of the oesophageal barrier pressure (BrP = LOSP − gastric pressure) leading to regurgitation of gastric contents during the perioperative period.[4] Therefore, this study was designed to compare the effects of halothane, isoflurane and desflurane on LOS tone in pigs using a manometric method.

Materials and methods

After obtaining approval from our institutional animal care committee, we studied 24 pigs (weight 22–25 kg). Ketamine 8 mg kg^{-1} was given i.m. as premedication and propofol 2 mg kg^{-1} i.v. for tracheal intubation. Neuromuscular blocking agents were not given during the study. The lungs of the pigs were ventilated mechanically by an Ohmeda ventilator incorporated into a Modulus CD integrated anaesthetic machine (Madison, WI, USA) with a tidal volume of 15 ml kg^{-1} at a ventilatory frequency of 12–15 bpm. Ventilation was adjusted to obtain normocapnia at baseline (end-tidal carbon dioxide partial pressure of 4.6–5.6 kPa), the fractional inspired concentration of oxygen was set at 0.60 and pulse oximetry (Sp_{O_2}) was monitored continuously using the Ohmeda oximeter attached to the tail of the pig. After measurement of baseline values for LOS pressures, pigs were allocated randomly to one of three groups: halothane ($n = 8$), isoflurane ($n = 8$) or desflurane ($n = 8$). The inhaled anaesthetic was introduced and end-tidal concentrations were maintained at 0.5, 1 and 1.5 MAC for 15 min. End-tidal concentrations of each volatile agent were fixed according to previous studies in pigs. End-tidal concentrations of 0.5, 1.0 and 1.5 MAC were 0.60%, 1.20% and 1.80% for halothane,[8] 1.05%, 2.10% and 3.10% for isoflurane[9] and 5%, 10% and 15% for desflurane.[10] Halothane, isoflurane and desflurane were vaporized using Ohmeda vaporizers (Fluotec 5, Isotec 5 and Tec 6; Steeton, WY, USA). End-tidal anaesthetic concentrations were measured using a calibrated respiratory gas analyser (Ohmeda, Madison, WI, USA).

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LOS PRESSURE MEASUREMENT

LOS and gastric pressures were measured with the pig supine using perfused polyethylene catheters connected to pressure transducers. Transducers were zeroed to the mid-chest position and calibrated using a water column before each measurement. Pressures were recorded using a multiple channel recording system. The first readings for LOSP were obtained 8–10 min after induction of anaesthesia. The method for LOS pressure measurements has been described previously[11]: catheters were perfused constantly with water by a low-compliance infusion pump at 1 ml min^{-1} (compliance 200 mm Hg min^{-1}). The high-pressure zone was detected with a pull-through technique.

DATA ANALYSIS

Results were expressed as mean (SD). Statistical significance was determined by one-way analysis of variance for repeated measures for intra-group comparisons and by two-way analysis of variance for repeated measures for inter-group comparisons (CSS statistica; Statsoft, Tulsa, OK, USA). When significance was found, a *post hoc* test (Newman–Keuls test) was used to determine where the differences lay. $P < 0.05$ was considered statistically significant.

Results

The effects of halothane, isoflurane and desflurane on lower oesophageal pressures and barrier pressures are shown in figure 1 and table 1.

Despite the fact that the mean values of LOSP in the isoflurane group were 24% and 22% greater than the mean values in the desflurane and halothane groups, respectively, there was no significant difference in LOSP at baseline between the three groups (halothane 19.4 (5.6) mm Hg; isoflurane 24.1 (6.4) mm Hg; desflurane 19.7 (3.8) mm Hg). Both halothane and isoflurane produced a dose-related decrease in LOSP whereas desflurane had no effect. This decrease was apparent at 1 MAC for halothane and isoflurane whereas none of the three anaesthetics decreased LOSP significantly at 0.5 MAC. At 1.5 MAC, LOSP values were approximately 72% of baseline values for halothane, 56% for isoflurane and 86% for desflurane.

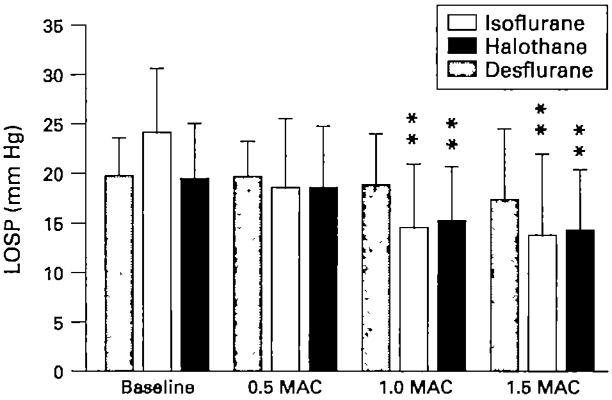

Figure 1 Effects of isoflurane, halothane and desflurane on lower oesophageal sphincter pressure (LOSP) at equipotent concentrations (mean, SD). $**P < 0.01$ compared with baseline.

Table 1 Effects of isoflurane, halothane and desflurane at 0.5, 1 and 1.5 MAC on oesophageal barrier pressure (mm Hg = lower oesophageal sphincter pressure – gastric pressure) (mean (SD)). $*P < 0.05$, $**P < 0.01$ compared with baseline; $†P < 0.05$ compared with desflurane and halothane (see text for P values < 0.05)

	Baseline	0.5 MAC	1.0 MAC	1.5 MAC
Isoflurane	15.4	10.2	5.6	5.8
	(5.0)	(5.2)*	(3.8)**†	(5.4)**†
Halothane	13.1	12.4	9.4	8.3
	(5.5)	(6.2)	(5.0)*	(5.2)**
Desflurane	12.0	11.4	11.1	10
	(5.8)	(4.9)	(5.8)	(6.0)

BrP decreased in parallel with the decrease in LOSP and this was significant at 0.5 MAC for isoflurane and 1.0 MAC for halothane. At 1.5 MAC, BrP values were approximately 62% of the baseline values for halothane, 37% for isoflurane and 83% for desflurane. Inter-group comparisons showed that BrP was not different at baseline and at 0.5 MAC. At 1.0 MAC the effect of isoflurane on BrP was significant different from desflurane ($P < 0.001$) and halothane ($P < 0.02$) whereas the effect of desflurane on BrP was not significantly different from halothane. At 1.5 MAC the effect of isoflurane on BrP was significantly different from desflurane ($P < 0.01$) and halothane ($P < 0.05$) whereas the effect of desflurane on BrP was not significantly different from halothane.

Discussion

We have demonstrated that a marked reduction in BrP occurred at 1 and 1.5 MAC of isoflurane and halothane whereas no changes were seen during administration of desflurane at equipotent MAC values.

Volatile anaesthetics have variable effects on LOSP and BrP. One study in humans reported that halothane and enflurane in combination with nitrous oxide decreased LOSP.[12] However, nitrous oxide was introduced before halogenated agents and it induced a more significant decrease in LOS pressure than after the introduction of halogenated agents. In addition, both agents were given at an inspiratory concentration of 2% without monitoring end-tidal anaesthetic concentrations. Giving the same inspiratory concentration of enflurane and halothane leads to different end-tidal concentrations (1.0 MAC is 0.29% for halothane in 50% nitrous oxide in oxygen and 0.57% for enflurane in 50% nitrous oxide in oxygen for humans). In contrast, one study performed in dogs showed that 1 h of exposure to 0.5–1% enflurane had no effect on LOSP.[13] However, this study was inconclusive because the MAC of the halogenated agent was not corrected for species (1.0 MAC of enflurane in dogs is 2.10%).

MAC values greater than 1.5 were impossible to obtain because of the design of the desflurane vaporizer. The Tec 6 vaporizer is manufactured for use in humans. MAC 2.0 is 12–14% in humans whereas it is approximately 20% in swine. The Tec 6 vaporizer does not allow inspiratory concentrations greater than 18%. Despite this, desflurane did not cause a significant decrease in BrP pressure at 1.5 MAC whereas isoflurane and halothane decreased BrP pressure at 1.0 MAC. There is no previous study on the effect of desflurane on BrP pressure to compare with our data. Failure of desflurane to affect BrP cannot be attributed to the difference in blood–muscle gas equilibration because BrP was measured after end-tidal concentrations of anaesthetic had been stable for 15 min. In humans, the blood–muscle partition coefficient of desflurane (2.02) is lower than those of halothane (3.4) and isoflurane (2.92).[14 15] Therefore, difference in equilibration between LOS muscle and end-tidal gas concentrations cannot explain the difference found. The absence of an effect of desflurane on LOS could be because of sympathetic nervous system activation which is known to occur when desflurane is administered alone.[16] In clinical practice, we usually use nitrous oxide to maintain anaesthesia. Because this agent decreases LOSP, its use may have attenuated the LOS responses observed during desflurane anaesthesia. Confirmation of this hypothesis requires a different study design.

The choice of anaesthetic technique and animal are probably important factors in the study of the effects of inhaled anaesthetics on LOS. Thus potential criticisms of our study design include the use of ketamine and propofol before administration of inhalation anaesthesia. However, ketamine is assumed not to influence LOSP.[11] In pigs, we showed recently that ketamine i.m. followed by propofol at a higher dose than that used in this study (5 mg kg^{-1} instead of 2 mg kg^{-1}) had no effect on LOS.[17] In addition, all animals received the same induction dose. As in humans, the musculature of the porcine LOS consists of smooth muscle fibres.[18] Moreover, it has been shown that the porcine LOS exhibits responses to various stimuli similar to that in humans.[19] Therefore, these results obtained in pigs could be applied to humans.

The lungs of all animals were ventilated mechanically before measurement of baseline LOS pressure and before introduction of the halogenated agents. This allowed us to obtain constant tidal volumes throughout the study. This is important because the pressure at the oesophago–gastric junction is created not only by contraction of the smooth muscles of the LOS but also by the striated muscle of the crural diaphragm.[20] All changes in pulmonary volumes could influence LOS recording. However, LOS pressures were measured at the end of expiration, a technique which minimizes the influence of respiration on LOS pressure recording.[4] Therefore, to compare LOS pressure from baseline to 1.5 MAC, the lungs of pigs were ventilated mechanically during baseline measurements.

In summary, in this animal study we have shown that in contrast with desflurane, both halothane and isoflurane decreased oesophageal barrier pressure. This finding may be clinically important in patients with a high risk of regurgitation.

Acknowledgements

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References

1. Reignier J, Ben Ameur M, Ecoffey C. Spontaneous ventilation with halothane in children. *Anesthesiology* 1995; **83**: 674–678.
2. Cheney FW, Posner KL, Caplan RA. Adverse respiratory events infrequently leading to malpractice suits. *Anesthesiology* 1991; **75**: 932–939.
3. Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane and desflurane during propofol-induced isoelectric electroencephalogram in humans. *Anesthesiology* 1995; **83**: 980–985.
4. Smith G, Dalling R, Williams TIR. Gastro–oesophageal pressure gradient changes produced by induction of anaesthesia and suxamethonium. *British Journal of Anaesthesia* 1978 ; **50**: 1137–1142.
5. Hall AW, Moossa AR, Clark J, Cooley GR, Skinner DB. The effect of premedication drugs on the lower oesophageal high pressure zone and reflux status of Rhesus monkeys and man. *Gut* 1975; **16**: 347–521.
6. Haddad JK. Relation of gastroesophageal reflux to yield sphincter pressures. *Gastroenterology* 1970; **58**: 1089–1090.
7. Roewer N. Can pulmonary aspiration of gastric contents be prevented by balloon occlusion of the cardia? A study with a new nasogastric tube. *Anesthesia and Analgesia* 1995; **80**: 378–383.
8. Weiskopf RB, Bogetz MS. Minimum alveolar concentrations (MAC) of halothane and nitrous oxide in swine. *Analgesia and Anesthesia* 1984; **63**: 529–532.
9. Moon PF, Scalett JM, Ludders JW, Conway TA, Lamb SV. Effect of fentanyl on the minimun alveolar concentration of isoflurane in swine. *Anesthesiology* 1995; **83**: 535–542.
10. Wedel DJ, Gammel SA, Milde JH, Laizzo PA. Delayed onset of malignant hyperthermia induced by isoflurane and desflurane compared with halothane in susceptible swine. *Anesthesiology* 1993; **78**: 1138–1144.
11. Cotton BR, Smith G. The lower oesophageal sphincter and anaesthesia. *British Journal of Anaesthesia* 1984; **56**: 37–46.
12. Senhati GH, Frey R, Star EG. The action of inhalation anaesthetics upon the lower oesophageal sphincter. *Acta Anaesthesiologica Belgica* 1980; **31**: 91–98.
13. Caldwell MPT, Marks P, Byrne PJ, Walsh TN, Hennessy TPJ. Hypotension induced by haemorrhage impairs lower oesophageal sphincter function. *British Journal of Surgery* 1994; **81**: 1517–1519.
14. Caldwell JE, Laster MJ, Magorian T, Heier T, Yasuda N, Lynam DP, Eger EI II, Weiskopf RB. The neuromuscular effects of desflurane, alone and combined with pancuronium or succinylcholine in humans. *Anesthesiology* 1991; **74**: 412–418.
15. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane and halothane in human tissues. *Anesthesia and Analgesia* 1989; **69**: 370–373.
16. Ebert TJ, Muzi M. Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. *Anesthesiology* 1993; **79**: 444–453.
17. Tournadre JP, Chassard D, Berrada KR, Boulétreau P. Effects of pneumoperitoneum on lower oesophageal sphincter. *British Journal of Anaesthesia* 1996; **76**: 130–132.
18. Weisbrodt NW. Neuromuscular organisation of esophageal and pharyngeal motility. *Archives of Internal Medicine* 1976; **136**: 524–531.
19. Goyal RK, Rattan S. Neurohumoral, hormonal and drug receptors for the lower esophageal sphincter. *Gastroenterology* 1978; **74**: 598–619.
20. Dodds WJ, Stewart ET, Hogan WJ, Stef JJ, Arndorfer RC. Effect of esophageal movement on intraluminal esophageal pressure recording. *Gastroenterology* 1974; **67**: 592–600.

British Journal of Anaesthesia 1996; 77: 784–785

SHORT COMMUNICATIONS

Distinguishing cerebrospinal fluid from saline used to identify the extradural space

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Summary

Because of the potential seriousness of unrecognized dural puncture during the performance of extradural analgesia and the widespread use of normal saline for the "loss of resistance" technique, it is important to differentiate between cerebrospinal fluid (CSF) and saline dripping from the extradural needle. During insertion of lumbar drains in 10 neurosurgical patients, we first identified the extradural space using saline for loss of resistance. Temperature (using the back of the gloved hand), pH, glucose and protein (using urine testing sticks) were tested by a blinded observer for ability to distinguish saline aspirated from the extradural space from CSF aspirated on establishing the dural puncture. Temperature, glucose and protein were independently 100% accurate in distinguishing saline from CSF. One saline sample had a pH value greater than 7 compared with nine CSF samples. We conclude that simple bedside testing for temperature, glucose, protein and pH accurately distinguished between CSF and saline used to identify the extradural space. (*Br. J. Anaesth.* 1996; **77**: 784–785)

Key words
Anaesthetic techniques, extradural. Cerebrospinal fluid. Spinal cord, extradural space.

Accidental dural puncture is a recognized complication of extradural anaesthesia.[1] It is important to recognize this immediately, as subsequent injection of local anaesthetic intended for the extradural space may produce unexpectedly extensive blocks.[2] Although dural puncture is indicated usually by free flow of cerebrospinal fluid (CSF) through the extradural needle, this may not always be the case, and CSF may drip only slowly from the needle hub.[3] If saline is used to identify the extradural space, using a "loss of resistance" technique, the anaesthetist may be uncertain if any clear fluid dripping from the needle is saline or CSF. Properties of CSF which have been used to identify it include temperature, glucose and protein content, pH and the absence of turbidity on mixing with thiopentone; however, these tests have been compared in relation to distinguishing CSF from local anaesthetic, for example after extradural anaesthesia.[4] In addition, the effect of injecting saline into the extradural space on the properties mentioned above has not been determined. As most dural punctures occur during placement of the extradural needle,[1] and saline is used more widely for loss of resistance than local anaesthetic solutions,[1] it would be more relevant clinically to compare these methods of distinguishing CSF from saline aspirated from the extradural space through the needle.

Methods and results

After obtaining medical Ethics Committee approval and informed consent, we studied patients undergoing neurosurgery that required insertion of a lumbar drain as part of the procedure (or as the actual procedure). General anaesthesia was induced according to the individual anaesthetist's preference (except in two patients who had insertion of lumbar drains only during local anaesthesia). The patient was then turned to the left lateral position and the extradural space identified with a 14-gauge lumbar drain needle using loss of resistance to saline. On identifying the extradural space, 10 ml of saline were injected in the space and 0.2–1.0 ml was aspirated into a 2-ml syringe. If none of the saline could be aspirated, another 5 ml of saline were injected and if still none could be aspirated the patient was excluded from the study. After aspirating saline, the needle was advanced through the dura and a similar volume of CSF was aspirated in another 2-ml syringe. Passage of the subarachnoid drain and further management continued as standard practice. The syringes were labelled as A or B according to randomly assigned instructions, and handed to a second investigator who was unaware of the allocation. The blinded investigator then immediately tested the temperature of a drop of the contents of each syringe on the back of his gloved hand to decide if it felt "warm" or "cold". Both fluids then were tested for glucose,

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Table 1 Results of stick testing of saline and cerebrospinal fluid (CSF) samples obtained through the Tuohy needle

Patient No.	Saline				CSF			
	Glucose	Protein	pH	Temp.	Glucose	Protein	pH	Temp.
1	0	0	5	Cold	+	++	8	Warm
2	0	0	5	Cold	+	+	8	Warm
3	0	0	7	Cold	+	++	8.5	Warm
4	0	0	7	Cold	+	+	7.5	Warm
5	0	0	7	Cold	+	+	7.5	Warm
6	0	0	7.5	Cold	+	++	5	Warm
7	0	0	6.5	Cold	Trace	++	8.5	Warm
8	0	0	5	Cold	Trace	++	8.5	Warm
9	0	0	5	Cold	Trace	+	8	Warm
10	0	0	6	Cold	Trace	++	8	Warm

protein and pH using urinary testing sticks. Data were analysed using Fisher's exact test.

Eighteen patients were recruited into the study. Eight were excluded because it was impossible to aspirate sufficient saline after an additional 5 ml of saline. The remaining 10 comprised six females and four males, mean age 45 (range 25–63) yr. The neurosurgical procedures carried out included five trans-sphenoidal hypophysectomies, two lumbar drain insertions, one transoral odontoidectomy, one transoral C1 biopsy and one excision of cervical neurofibroma.

The results of temperature and stick testing are shown in table 1. None of the saline samples tested positive for glucose or protein or was warm to the touch, compared with all 10 of the CSF samples ($P=0.0001$, two-tailed Fisher's exact test). One saline sample had a pH value >7, compared with nine CSF samples ($P=0.0001$, two-tailed Fisher's exact test). There were no incidences of bloody tap.

Comment

Anaesthetists have used different techniques for distinguishing saline from CSF during identification of the extradural space using saline for the loss of resistance test. Observation of free flow of CSF alone has been shown to be unreliable.[3] In this study, despite its small size, we have demonstrated that subjective testing for temperature of the fluid and simple bedside objective testing using urinary testing sticks can reliably distinguish CSF from saline, even when obtained from the extradural space. Although dural puncture in our study was produced with a 14-gauge needle, there is no reason to suppose the results would be different if a 16-gauge needle had been used.

Although saline normally does not contain glucose or protein, a positive test may theoretically result from blood contamination or CSF diffusion to the extradural space.[5] Our study showed that even on injection of saline into the extradural space it still tested negative for both. Earlier studies that tested for glucose to differentiate CSF from local anaesthetic injected previously into the extradural space showed that positive testing for glucose did not necessarily imply that the tested fluid was CSF.[4,5] The consistent result of glucose testing in our study may represent different properties of local anaesthetic solutions and saline, or because saline was aspirated immediately after injection, thus not providing sufficient time for contamination with glucose from the extradural space or vessels. Alternatively, injection of 10 ml of saline into the extradural space may have diluted any contamination with glucose or protein. However, of interest is the fact that even after injection of this volume and an additional 5 ml, eight patients had to be excluded because insufficient volume of saline could be aspirated. We have no explanation for the variation in saline pH values obtained; the same manufacturers' products (both saline and testing strips) were used in all cases. It is possible that for estimation of pH using testing strips, subjective judgement as to which of the manufacturer's supplied colour bands best matches the sample's indicator colour is less reliable than with the other tests.

Finally, it is important to emphasize that this study showed that testing for only temperature, glucose, protein and pH were useful at the time of identifying the extradural space with the needle. The use of aspiration testing and the test dose of local anaesthetic after insertion of the catheter are still mandatory.

References

1. Stride PC, Cooper GM. Dural taps revisited. *Anaesthesia* 1993; 48: 247–255.
2. Morgan B. Unexpectedly extensive conduction blocks in obstetric extradural analgesia. *Anaesthesia* 1990; 45: 148–152.
3. Holloway TE, Telford RJ. Observations on deliberate dural puncture with a Tuohy needle: depth measurements. *Anaesthesia* 1991; 46: 722–724.
4. Tessler MJ, Wiesel S, Wahba RM, Quance DR. A comparison of simple identification tests to distinguish cerebrospinal fluid from local anaesthetic solution. *Anaesthesia* 1994; 49: 821–822.
5. Waters JH, Ramanathan S, Chuba JV. Glucose in extradural catheter aspirate. *Anesthesia and Analgesia* 1993; 76: 546–548.

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Use of a pneumatic tourniquet induces changes in central temperature†

J.-P. ESTEBE, A. LE NAOURES, Y. MALLEDANT AND C. ECOFFEY

Summary

Twenty-six patients requiring orthopaedic surgery were anaesthetized and oesophageal and rectal temperature were monitored continuously. Twenty patients requiring a pneumatic tourniquet were allocated prospectively to one of two groups: passive group (Pg) with reflective insulation on all available skin surface ($n=10$) and forced group (Fg), with active warming by a forced air system ($n=10$). Six patients without a tourniquet were used as a reference group (Rg). The pneumatic tourniquet time was similar in the tourniquet groups. During tourniquet inflation, oesophageal temperature increased with time. The difference was significant compared with the reference group at approximately 20 min. At about 30 min, oesophageal temperature in group Fg was significantly higher than that in group Pg. After tourniquet deflation, temperature decreased transiently. Changes in rectal temperature were similar but delayed significantly. A mechanism to explain the increase in core temperature during pneumatic tourniquet use remains unclear. A redistribution mechanism by cooling of the blood in a cold and vasodilated limb could explain the decrease of temperature after tourniquet deflation. (*Br. J. Anaesth.* 1996; **77**: 786–788)

Key words
Surgery, orthopaedic. Equipment, tourniquets. Temperature, monitoring.

The use of a pneumatic tourniquet for "bloodless-field" surgery is common in orthopaedic practice. However, its use is known to cause many adverse effects[1]: it has been noted that central temperature increases progressively in paediatric patients while the limb tourniquet is inflated,[2 3] but not in adults. On the other hand, a significant decrease in core temperature occurs abruptly after tourniquet release.[4]

In order to clarify temperature changes during tourniquet use, we have compared oesophageal and rectal temperatures during and after a prolonged period of tourniquet inflation in adults.

Methods and results

We studied 26 male adult patients (range 18–45 yr), ASA PS I–II, undergoing orthopaedic surgery. The study was approved by the local Ethics Committee and informed written consent was obtained from each patient. Patients were healthy and none was taking medication. They had no evidence of infection and were not given blood or blood products.

Twenty of 26 patients were scheduled prospectively for fixation of a single lower extremity fracture using the pneumatic tourniquet for a prolonged period (>60 min). Patients with multiple trauma or short periods of tourniquet inflation were excluded. After induction of general anaesthesia, an 8-cm tourniquet cuff was applied around the upper thigh of the operative limb. For exsanguination, the leg was elevated for 5 min at 45° before tourniquet inflation. Arterial flow was occluded with a pressure of 350 mm Hg. For ethical reasons, the reference group (Rg) was studied without randomization and served only as a standard reference. Successively, six patients were included in group Rg: three patients undergoing the same surgery but with tourniquet contraindications (skin lesion or excessive oedema) and three patients where a tourniquet was not indicated (intramedullary nailing of shaft fractures of the tibia).

Premedication was not given and anaesthesia was induced with thiopentone 4–6 mg kg^{-1} i.v. and fentanyl 3 $\mu g\ kg^{-1}$ i.v. No neuromuscular blocking agents were used. After tracheal intubation, the lungs were ventilated mechanically with 60% nitrous oxide in oxygen in a semi-closed system without any volatile anaesthetic. Additional doses of fentanyl (5–10 $\mu g\ kg^{-1}\ h^{-1}$) or thiopentone (1.3–2.5 mg $kg^{-1}\ h^{-1}$) were given as needed. A minimal infusion of lactated Ringer's solution at room temperature was given. Ambient temperature was controlled at 20 °C. For all patients, routine monitoring included electrocardiography, pulse oximetry, end-tidal carbon dioxide and arterial pressure measurements.

Twenty patients were allocated randomly to one of two groups using a sealed envelope technique. In

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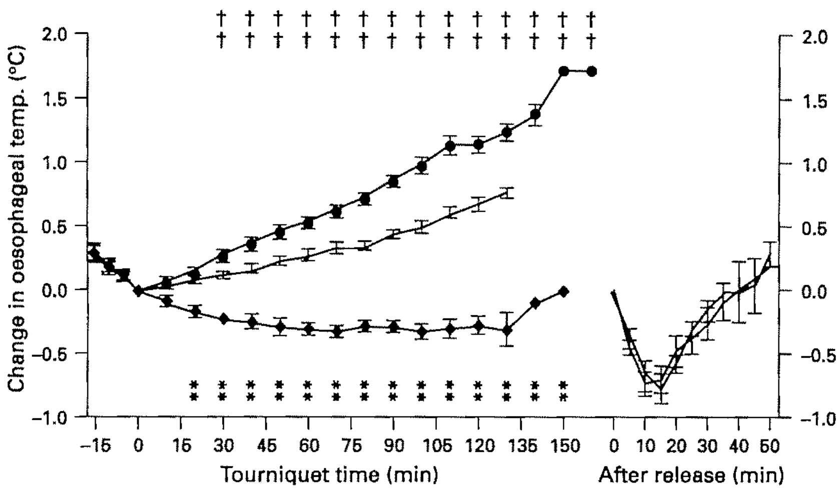

Figure 1 Change in oesophageal temperature (mean, SEM) in patients with a tourniquet undergoing active warming (group Fg) (●) or passive insulation (group Pg) (–) and in patients without a tourniquet (group Rg) (◆). Time zero for temperature reference was tourniquet inflation time whereas core temperature was measured continuously as soon as possible after induction (for the control group time zero was surgical incision). After tourniquet release a new time zero for temperature reference was the time of release of the tourniquet. $^{**}P<0.01$ group Rg *vs* group Pg; $^{\dagger\dagger}P<0.01$ group Pg *vs* group Fg.

the passive group (group Pg, $n=10$) the available skin surface was covered with passive reflective insulation material. In the forced group (group Fg, $n=10$) patients were covered by an active warming system (forced air system: Bair Hugger 500E Augustin medical SA at 38 °C with full body 300 blanket). Group Rg was treated with the same active warming procedure. As soon as possible after induction, core temperature was measured simultaneously in the lower third of the oesophagus and rectally with thermistor probes (Hewlett Packard 21075 A probe). Both temperatures were monitored (Hewlett Packard 78364 C monitor) continuously until the end of surgery. There was no intervention which could have changed the temperature.

Data are expressed as mean (SEM) and analysed using ANOVA with repeated measures. Regression analysis and the Mann–Whitney *U* test, and the Kruskal-Wallis test for non-parametric data, as appropriate, were used to determine significance ($P<0.05$).

Patient characteristics were comparable for all three groups. Tourniquet times were similar (106 (7) min and 115 (7) min for groups Pg and Fg, respectively). Initial temperatures after induction of anaesthesia were comparable. All patients had an initial rectal temperature (37.1 (0.1) °C) significantly higher ($P<0.01$) than the oesophageal temperature (36.6 (0.2) °C).

Changes in oesophageal temperature before, during and after tourniquet inflation are shown in figure 1. Before tourniquet inflation, temperature decreased similarly. Exsanguination had no significant effect. Patients in group Rg remained nearly normothermic throughout surgery. In contrast, core temperature increased significantly in both tourniquet groups and exceeded reference values at all times after 20 min had elapsed. Increases in group Fg were significantly greater than those in group Pg at all times after 30 min had elapsed. This central temperature increase correlated ($P<0.001$) with tourniquet time ($r=0.98$ and $r=0.99$ for groups Pg and Fg, respectively). Immediately after tourniquet deflation, core temperature decreased similarly in both tourniquet groups. The maximum mean decrease, 10–15 min after tourniquet deflation, was 0.7 (0.1) °C. This decrease did not correlate significant with tourniquet duration and was transient.

Changes in rectal temperature were similar but with a significant delay compared with oesophageal changes. In the tourniquet groups, pelvic temperature increased and was significantly higher than that in group Rg at all times after 50 min had elapsed. Increases in group Fg were significantly higher than those in group Pg at all times after 70 min had elapsed. This increase correlated with time ($r=0.93$ and $r=0.96$ for groups Pg and Fg, respectively; $P<0.001$). After tourniquet deflation, rectal temperature did not change.

Progressively, in both tourniquet groups, arterial pressures increased significantly (systolic arterial pressure before tourniquet 111 (18) mm Hg and before release 150 (18) mm Hg, diastolic arterial pressure before tourniquet 59 (13) mm Hg and before release 89 (12) mm Hg; $P<0.01$). After release, pressures decreased significantly to a minimal level obtained 3–10 min after tourniquet release ($P<0.01$). There was a significant difference in end-tidal carbon dioxide concentration between the level just before tourniquet release (4.3 (0.3) kPa) and the peak 3–8 min after tourniquet release (5.9 (0.4) kPa; $P<0.01$). There was no difference between tourniquet groups and no correlation with tourniquet time. All of these variations returned to normal 20 min after tourniquet release.

Comment

In this study the duration of tourniquet inflation appeared to be the main precipitating factor for the increase in core temperature. This increase correlated with duration of tourniquet inflation. It was similar to that reported in previous paediatric studies where there was no significant difference between smaller and larger children,[2 3] but it has not been described previously in adults. We have found similar changes in adults, with the greatest changes in patients who were actively warmed.

Oesophageal temperature is monitored commonly in patients receiving general anaesthesia. It is considered a true measure of core temperature and it responds rapidly to changes in body temperature. Conversely, rectal temperature correlates poorly with core temperature and has a significantly delayed response because of cooling by the legs. In our study, in all patients, initial rectal temperature was significantly higher than oesophageal temperature because of two possible mechanisms: delay in perioperative hypothermia developing and warming by blood as it returned from the traumatized leg. There was a delay when comparing changes in rectal temperature with oesophageal temperature but hyperthermia was not greater with rectal measurements.

We postulate that the increase in core temperature during tourniquet inflation was caused by slow release of ischaemic metabolites from the extremity into the systemic circulation, using vascular bone as a tourniquet bypass.[3] However, when heat loss to the environment decreases because of reduced surface area while the level of heat production remains stable, core temperature may increase. But, as observed in children, hyperthermia was greater than predicted from the reduction in effective surface area.[2] In fact, if the surface area of each leg constitutes approximately 18% of the total body surface area, the estimated mass of the leg was approximately 16% in adults.[5] It has been suggested that tourniquet ischaemia may initiate a reaction similar to that of malignant hyperthermia.[6]

After tourniquet release, core temperature decreased rapidly but transiently. This significant decline has been described previously in adults[4] and was explained by redistribution with cooling of blood in a cold and vasodilated limb. Further studies may confirm that postoperative hyperthermia could be explained, in part, by tourniquet use. We also observed other adverse effects such as an increase in arterial pressure during tourniquet use and an increase in end-tidal carbon dioxide at tourniquet deflation.

Acknowledgements

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References

1. Estebe J-P, Malledant Y. The pneumatic tourniquet in surgery of the limb. *Annales Françaises d'Anesthésie et de Réanimation* 1996; **15**: 162–178.
2. Bloch EC, Ginsberg B, Binner RA, Sessler DI. Limb tourniquets and central temperature in anesthetized children. *Anesthesia and Analgesia* 1992; **74**: 486–489.
3. Goodarzi M, Shier N-H, Ogden J A. Physiologic changes during tourniquet use in children. *Journal of Pediatric Orthopedics* 1992; **12**: 510–513.
4. Dos Reis A jr. Tourniquet use and intraoperative hypothermia. *Anesthesia and Analgesia* 1989: **69**: 549–550.
5. Kurz A, Sessler DI, Christensen R, Dechert M. Heat balance and distribution during the core-temperature plateau in anesthetized humans. *Anesthesiology* 1995; **83**: 491–499.
6. Myles P. Thigh tourniquet, a trigger for MH. *Anaesthesia and Intensive Care* 1993; 21: 255.

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CASE REPORTS

A modification of sub-mental intubation

J. D. GREEN AND U. J. MOORE

Summary

In patients who have sustained base of skull fractures, the mode of intubation is controversial, with many anaesthetists arguing against nasal intubation. In several maxillofacial procedures temporary intermaxillary fixation (IMF) in the intra-operative period may be essential to achieve optimal results in fixation. For patients with combined facial and base of skull injury, tracheotomy may have to be performed. The submental approach to intubation allows IMF to be used without resort to nasal intubation or tracheotomy. We describe a modification of the original technique which is applicable to any reinforced tracheal tube and which does not compromise the airway. (*Br. J. Anaesth.* 1996; **77**: 789–791)

Key words
Intubation tracheal, technique. Complications, maxillofacial injuries.

Nasal tracheal intubation after severe craniomaxillofacial trauma can result in the passage of the tracheal tube into the cranium, with consequent brain damage.[1 2] To avoid this complication, oral intubation may be preferred but this may severely compromise maxillofacial repair because of interference with the placement of intermaxillary fixation (IMF), which is used to establish the patient's occlusion in the intraoperative period. In many facial fractures, particularly those involving the maxilla, this is an essential guide to optimal fracture reduction and fixation. To enable IMF to be placed, tracheotomy may be indicated but this carries significant morbidity.[3 4] The use of the submental route for tracheal intubation has been described[5 6] and provides a useful alternative route in the severely traumatized patient in whom establishment of intra-operative IMF is preferred. The technique, as described originally, involves insertion of an oral tube, the free end of which is then exteriorized through a submental incision and reconnected. This involved the use of a reinforced tracheal tube in which the universal connector was removed easily for passage through the submental tissues. These tubes are not always available in the operating room and a technique is described below to allow the use of this technique with tubes in which the universal connector is non-removable. A case report illustrates the clinical use of this technique.

MODIFIED TECHNIQUE FOR SUBMENTAL INTUBATION

The trachea is intubated via the oral route and a 2-cm submental skin incision is made close to the lower border of the mandible. Blunt dissection is carried out as close as possible to the inner aspect of the mandible into the floor of the mouth. An incision is then made in the floor of the mouth sufficient to allow the passage of a suitable tracheal tube. During dissection care should be taken to ensure no damage occurs to the facial nerve, lingual nerve or submandibular duct. Artery forceps may now be passed from the floor of the mouth out through the extra-oral incision to grasp a suitable tracheal tube which may then be drawn through the wound into the mouth. The original oral tube may now be withdrawn and the second tube substituted. When the cuff is inflated and a throat pack inserted, temporary sutures are placed to stabilize the tube. At the end of the procedure the process may be reversed to re-establish the oral route, and closure of the extra-oral wound may be achieved. However, the tube may be left *in situ* and removed subsequently, as described originally.[5]

Case report

A 26-yr old security officer was admitted to the accident and emergency department of the Newcastle General Hospital after being found unconscious at the bottom of a ladder. He had sustained head and facial injuries. On admission he was conscious with a Glasgow coma score of 10 (motor 5, eyes 1, verbal 4). He was amnesic of the event. On examination there was severe facial swelling and bruising, with a large supraorbital haematoma, left-sided rhinorrhoea and epistaxis. Both pupils responded to light; the left eye however showed a pulsatile exophthalmos with the globe displaced inferolaterally. The maxilla was freely mobile with the left zygoma displaced, and there appeared to be a comminuted fracture of the naso–ethmoid complex.

Radiographic examination confirmed extensive facial fractures. Because of the pulsation in the left

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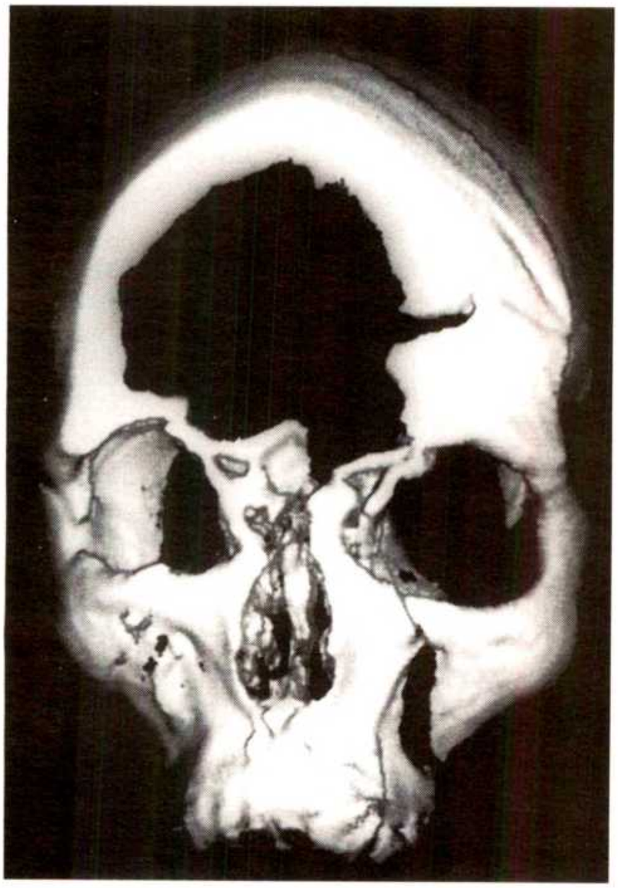

Figure 1 CAT scan: three-dimensional reconstruction showing the extensive nature of the facial injuries. The naso–ethmoidal fracture can be seen in continuity with the cranial base.

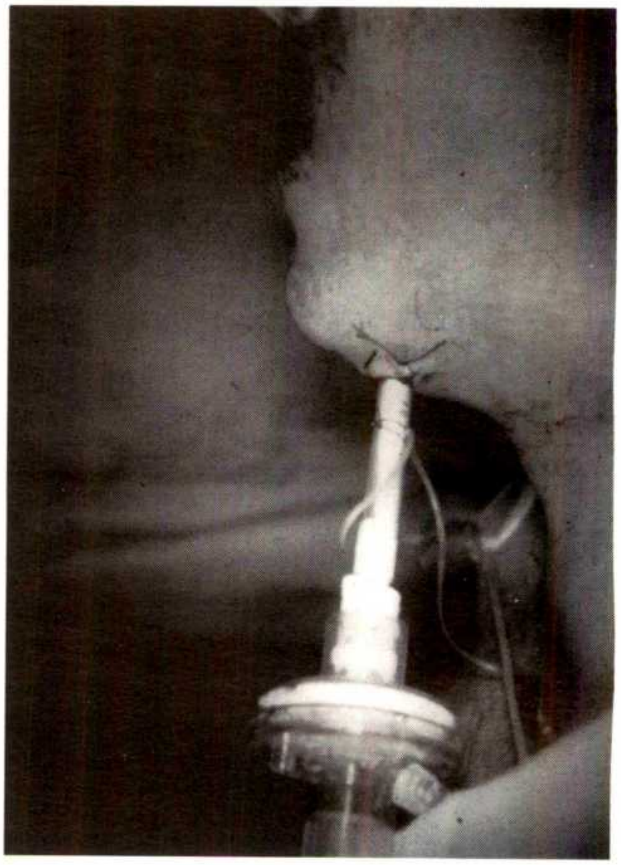

Figure 2 Photograph showing submental intubation with the tracheal tube sutured in position.

orbit a carotid angiogram was performed. This was normal with no evidence of a carotid–cavernous sinus.

Computer axial tomography (fig. 1) showed a fractured frontal bone in continuity with the left orbital roof, anterior comminution of the naso–ethmoidal complex and displacement of the left zygoma. There were also maxillary fractures with a Le Fort II fracture on the right and a Le Fort III fracture on the left. These injuries can be seen in the three-dimensional reconstruction from the CAT scan (fig. 1).

The patient was observed for 3 days while his level of consciousness improved, however the rhinorrhoea persisted and repair of the dural tear and the maxillofacial injuries were scheduled in a combined procedure. In order to achieve optimal surgical repair, application of IMF was preferred but the presence of basal skull fractures rendered nasal intubation potentially complicated. In order to avoid tracheotomy we elected to perform a modified submental intubation.

The patient's lungs were preoxygenated for 4 min after which anaesthesia was induced with fentanyl 200 μg and thiopentone 350 mg. Airway security was confirmed and, having shown that hand ventilation of the lungs was possible, vecuronium 10 mg were administered. Oral intubation was produced by passing a 9-mm id cuffed tracheal tube.

A 2-cm incision was made in the left submental region parallel to the lower border of the mandible which was extended intraorally. A 7-mm id reinforced tracheal tube was then passed through the incision from the exterior and manoeuvred with McGill forceps so that it was positioned in the oropharynx. The oral tracheal tube was then removed and the patient's trachea intubated with the submental tube. This was sutured in position extra-orally and the mouth packed (fig. 2).

Craniotomy and dural repair were performed, the orbital roof was explored and then the maxillary fractures reduced, arch bars having been wired around the upper and lower teeth, and the occlusion established. At the end of the procedure the tracheal tube was replaced with a conventionally positioned oral tube so that the incision could be sutured and closed. Neuromuscular block was antagonized with glycopyrronium 500 μg and neostigmine 2.5 mg. The patient was allowed to regain consciousness and, after confirmation of airway security, the trachea was extubated. Postoperative recovery was unremarkable, and the operative result was satisfactory. The submental scar at 6 weeks was minimal.

Discussion

Altermir[5] first described the submental route for tracheal intubation in 1986. The technique allows a patient's trachea to be intubated for maxillo-mandibular fixation and avoids nasal intubation and tracheotomy. More recently, Gordon and Tolstunov[6] have described the technique in the management of two patients. We have described how the technique was modified in the management of a patient with severe head and facial trauma. With the Mallinkrodt tracheal tube used in the US, the universal connector can be removed easily from the tube.

In past descriptions of the submental approach, the authors have performed oral intubation, removed the connector and passed the tracheal tube through the incision from interior to exterior, while the tracheal tube has been in the larynx. In this case a second tube was used, having first secured the airway with a conventionally placed oral tracheal tube. The reasons for this were two-fold. First, there was less risk of compromising the patient's airway if difficulties were encountered re-attaching the connector or passing the tube through the incision. Second, with the tube used, a Mallinkrodt Medical Safety-Flex, the manufacturer's design specifically prevents the removal of the universal connector, as does the Flexicare Medical, Reinforced Murphy tracheal tube. The procedure proved straightforward and was not associated with any marked bleeding from the incision or compromise of the patient's airway.

The modification described provides a safe alternative technique when oral intubation interferes with the surgical approach in the treatment of severe craniomaxillofacial injury.

References

1. Hall DB, Nasotracheal intubation with facial fractures. *Journal of the American Medical Association* 1989; **261**: 1198.
2. Zmyslowski WP, Nasotracheal intubation in the presence of facial fractures. *Journal of the American Medical Association* 1989; **262**: 1327.
3. Lewis RJ. Tracheostomies. Indications, timing and complications. *Clinics in Chest Medicine* 1992; **13**: 137–149.
4. Zeitouni AAG, Kost KM. Tracheostomy; a retrospective review of 281 cases. *Journal of Otolaryngology* 1994; **23**: 61–66.
5. Altermir H. The submental route for endotracheal intubation: a new technique. *Journal of Oral Maxillofacial Surgery* 1986; **14**: 64.
6. Gordon NC, Tolstunov DDS. Submental approach to oroendotracheal intubation in patients with midfacial fractures. *Oral Surgery, Oral Medicine, and Oral Pathology* 1995; **79**: 3.

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Hepatic rupture complicating eclampsia in pregnancy

S. KARADIA, C. WALFORD, M. MCSWINEY AND M. S. NIELSEN

Summary

We describe hepatic rupture in a 37-yr-old woman admitted to the intensive care unit after an eclamptic convulsion. The intensive care and surgical management are discussed. (*Br. J. Anaesth.* 1996; **77**: 792–794)

Key words
Complications, hepatic. Complications, disseminated intravascular coagulation. Complications, eclampsia. Liver, transplantation. Intensive care.

Hepatic rupture is a rare complication of pre-eclampsia or eclampsia. It may present with lower chest or upper abdominal pain. Hepatic rupture may be associated with disseminated intravascular coagulation (DIC) and subsequent haemorrhage. In unremitting hepatic failure, transplantation may have to be considered if other treatments fail to control haemorrhage.

Case report

A healthy 37-yr-old primigravida was admitted to hospital 12 days post-term for induction of labour after a previously uncomplicated pregnancy. Arterial pressure was 120/72 mm Hg, haemoglobin concentration 126 g litre^{-1} and platelet count 236×10^{9} litre^{-1}. Multistix urinalysis was negative for protein. Labour was induced using dinoprostone pessaries and proceeded uneventfully for 4 h during which time the patient satisfactorily self-administered Entonox and used TENS for analgesia. No further requests for additional analgesia were made. Two hours before delivery she complained of severe lower chest pain. The patient was not cyanosed and arterial pressure and heart rate were normal. Clinical examination and electrocardiography were unremarkable. The pain stabilized after administration of pethidine 75 mg i.m. One hour later the patient suffered a grand mal convulsion. The convulsion was controlled with diazepam 7.5 mg i.v.

Vaginal examination revealed a fully dilated cervix with the fetal head 2 cm below the ischial spines. Neville Barnes forceps were applied and a healthy male infant was delivered. Manual removal of an incompletely separated placenta resulted in loss of 500 ml of blood. An episiotomy wound was repaired. After delivery the patient's arterial pressure was 180/105 mm Hg and urine was found to contain 2+ of protein on Multistix urinalysis (equivalent to 1 g litre^{-1}).

Eclampsia was diagnosed and i.v. magnesium sulphate was commenced in a dose of 5 g followed by an infusion of 1 g h^{-1}. Haemoglobin concentration was 135 g litre^{-1}, white cell count 22.5 g litre^{-1} and platelet count 101×10^{9} litre^{-1}. Invasive monitoring of arterial and central venous pressures was commenced in addition to pulse oximetry and urine output. Before transfer to the intensive care unit (ICU) the patient suffered a post-partum haemorrhage of 1500 ml requiring an emergency examination under anaesthesia. After anaesthesia, gynaecological examination revealed generalized oozing of blood from the external genitalia with an atonic uterus filled with blood clot. The blood clot was removed and bimanual pressure exerted to achieve uterine contraction. A vaginal pack was inserted to help tamponade the haemorrhage. Blood loss with this procedure was approximately 1000 ml. A continuous infusion of Syntocinon at a rate of 10 u. h^{-1} was commenced to maintain uterine contraction. A full blood count at this stage revealed a haemoglobin concentration of 96 g litre^{-1} and a platelet count of 62×10^{9} litre^{-1} with an international normalized ratio (INR) of 4. The patient received 6 u. of blood and 6 u. of platelets. A dopamine infusion of 3 μg kg^{-1} min^{-1} was commenced and urine output remained at 1 ml kg^{-1} h^{-1}.

The patient was transferred, with her trachea still intubated and her lungs ventilated, to the ICU for further monitoring of haematological and vital signs. She was sedated with an infusion of midazolam 50 μg kg^{-1} h^{-1} and morphine 30 μg kg^{-1} h^{-1}. No further convulsions occurred.

Repeated infusion of FFP, platelets, cryoprecipitate and colloid were administered to maintain normovolaemia and coagulation function. An infusion of aprotinin 200 000 u. h^{-1} was commenced after a loading dose of 1 000 000 u. Six hours after admission to the ICU the patient became hypotensive and developed a distended abdomen. An ultrasound scan showed intraperitoneal fluid and mixed reflectivity in the region of the liver capsule, suggesting haemorrhage. After further prompt fluid resuscitation, laparotomy was performed. At operation a sheared rupture of the right lobe of the liver was

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found. The liver substance showed generalized fatty infiltration and petechiae. Only limited haemostasis was achieved and the peritoneal cavity was packed and the abdomen closed. After operation she was transferred back to the ICU where she continued to show cardiovascular and haematological signs of haemorrhage. Systolic arterial pressure was now persistently low at 90 mm Hg with a tachycardia of 110 beat min^{-1} and a decreasing urine output. Haemoglobin concentration was 96 g dl^{-1} despite 22 u. of blood, platelet count 46×10^9 litre^{-1} despite 20 u. of platelets and INR was 2.4. A further laparotomy revealed a right subcapsular haematoma of the liver. A right hemihepatectomy was performed as the only means of achieving haemostasis; subsequent histology showed diffuse necrosis of the architecture of the liver.

After operation a pulmonary artery catheter was inserted. Cardiac index was 2.1 litre min^{-1} m^{-2} with a pulmonary artery wedge pressure of 11 mm Hg. Dobutamine was commenced at a rate of 5 μg kg^{-1} min^{-1} which produced a cardiac index of 4.5 litre min^{-1} m^{-2}. Further volume replacement was necessary to maintain cardiac filling pressure.

Despite an eventual blood transfusion of more than 120 u., an infusion of 20 u. of cryoprecipitate, 42 u. of platelets and 48 u. of FFP, haemostasis was not achieved and the INR remained greater than 1.5. Two further laparotomies were performed to evacuate the intraperitoneal blood clot, replace intra-abdominal packs and attempt haemostasis. A subcapsular haematoma of the remaining left lobe of the liver had developed which was treated conservatively.

As all conventional means of controlling haemorrhage had failed, the patient was referred to a supra-regional liver unit for consideration of transplantation as a means of controlling bleeding. She was accepted and transferred using the intensive care transport system. The patient remained stable throughout the journey, requiring only 3 u. of blood. On arrival the patient remained stable for 24 h when a further laparotomy was performed to remove the intra-abdominal packs, evacuate the haematoma and to administer argon diathermy to the raw surface of the left lobe of the liver. At this time the vaginal packs were removed and the uterus and external genitalia examined; there was no further oozing of blood from these sites. After operation she was haemodynamically stable, her INR remained in the range 1.2–1.5 and renal function was satisfactory, with a urine output of 1 ml kg^{-1} h^{-2}. Under these circumstances liver transplant was considered unnecessary.

Over the subsequent 5 weeks the patient continued to improve despite requiring treatment for intermittent sepsis and mild ARDS. The patient returned to her original hospital where she was reunited with her baby.

Discussion

Our patient developed eclampsia without any preceding features of pre-eclampsia. Douglas and Redman reported recently that 38% of eclamptic cases were unheralded by hypertension and proteinuria.[1] They stated that convulsions are one of a range of clinical features caused by endothelial cell damage secondary to placental ischaemia. The manifestations of the syndrome depend on the site and extent of endothelial cell damage and are not the result of a predetermined hierarchy. Convulsions may precede hypertension or proteinuria, as demonstrated in this case.

The aetiology of the pre-eclampsia complex of hypertension, proteinuria and convulsions is unknown. DIC may occur and its severity is thought to be proportional to the degree of pre-eclampsia. DIC is a result of unregulated release of free thrombin into the circulation.[2] Tissue factor is released locally at the site of tissue damage and this complexes with factor VII which results in a cascade of enzymic reactions required for thrombin generation. Damaged placental endothelium is unable to concentrate antithrombin on its surface which normally would prevent build up of thrombin. This results in widespread microvascular thromboses leading to organ damage. To maintain vascular patency, excess plasmin is generated causing fibinolysis and fibrinogenolysis. Generation of free thrombin and plasmin results in thrombotic and haemorrhagic manifestations, respectively, of DIC.

Additionally, free thrombin results in a change in platelets such that their surfaces bind and concentrate all the components of the haemostatic system. Platelet survival and numbers are reduced. Haemorrhage is the commonest manifestation of DIC because of generation of free plasmin and depletion of coagulation factors and platelets.

Eclamptic patients are prone to spontaneous haemorrhages and frequently show fibrin deposition on the basement membrane of hepatic sinusoids and arterioles. It has been postulated that sensitization of the reticuloendothelial system of the liver by previous subclinical pre-eclampsia may render it unable to clear fibrin thrombi from the circulation. As a result, infarction with vascular disruption may occur leading to intrahepatic haemorrhage and parenchymal destruction. Rarely the periportal necroses that result coalesce and form subcapsular haematoma and ultimately rupture of Glisson's capsule with intraperitoneal haemorrhage.[3] This may be exacerbated by diaphragmatic and abdominal muscular contractions but the underlying hepatic parenchyma is abnormal and a history of significant trauma can rarely be elicited.

Concerning the early diagnosis of spontaneous hepatic rupture, Howard and Jones claimed that the most important presenting complaint is right upper quadrant pain and that ultrasound scan is the quickest means of diagnosis, although computerized tomography is more sensitive.[4] Our patient complained of lower central chest pain and an ultrasound scan demonstrated the presence of intraperitoneal fluid with mixed reflectivity around the hepatic area. Howard and Jones also stated that in such cases termination of pregnancy is the first step in the treatment and that surgery may not be required. They also stated that although elevated transaminase concentrations, decreased platelets and DIC occur acutely, they resolve rapidly.[5] This was not found to be the case with our patient who, despite aggressive medical and surgical treatment, continued to show signs of bleeding and DIC.

Loevinger, Lee and Anderson reported a patient in whom transcatheter gelfoam embolization of the hepatic artery was successful in arresting intrahepatic haemorrhage after hepatic rupture.[6] They claimed that this is an alternative to surgery if the patient is clinically stable. We believe that our patient would not have been.

In a review of four cases between 1973 and 1976, Nelson, Archibald and Albo[7] found that all four continued to require significant blood replacement of 4–25 u. after laparotomy for hepatic rupture. Erhard and colleagues reported the case of a 30-yr-old primigravida who developed hepatic rupture as a complication of the HELLP syndrome (haemolysis, elevated hepatic enzymes, low platelets) who successfully underwent urgent hepatic transplantation after a hepatectomy for bleeding and hepatic necrosis.[8] Nelson, Archibald and Albo claimed that the lesion most often described is subcapsular haematoma of the right hepatic lobe with free rupture into the peritoneal cavity and resultant exsanguinating haemorrhage.[7]

Hepatic rupture, although a rare complication of eclampsia, carries a high mortality rate. In some review series this was between 60 and 70%.[9] Hence when the triad of pre-eclampsia, right upper quadrant pain and sudden hypotension is present in pregnancy or shortly afterwards, prompt recognition is essential. Ultrasound scan should be performed to aid diagnosis, and transplantation should be considered if medical and surgical intervention fails to control bleeding. Any woman who develops DIC during or after labour must be admitted to an intensive care unit or a high dependency unit for monitoring.[10]

References

1. Douglas KA, Redman CWG. Eclampsia in the United Kingdom. *British Medical Journal* 1994; **309**: 1395–1400.
2. Baglin T. Disseminated intravascular coagulation: diagnosis and treatment. *British Medical Journal* 1996; **312**: 683–687.
3. Castaneda H, Garcia-Romero H, Canto M. Hepatic hemorrhage in toxemia or pregnancy. *American Journal of Obstetrics and Gynecology* 1970; **107**: 578–584.
4. Howard EW, Jones HL. Massive hepatic necrosis in toxemia of pregnancy. *Texas Medicine* 1993; **89**: 74–80.
5. Utley JR. Spontaneous rupture of the liver during pregnancy. *Surgical Gynaecology and Obstetrics* 1971; **133**: 250–252.
6. Loevinger EH, Lee WM, Anderson MC. Hepatic rupture associated with pregnancy: treatment with transcatheter embolotherapy. *Obstetrics and Gynecology* 1985; **65**: 281–284.
7. Nelson EW, Archibald L, Albo D. Spontaneous hepatic rupture in pregnancy. *American Journal of Surgery* 1977; **134**: 817–820.
8. Erhard J, Lange R, Niebel W, Scherer R, Kox WJ, Phillip T, Eigler FW. Acute liver necrosis in the HELLP syndrome: successful outcome after orthotopic liver transplantation. *Transplant International* 1993; **6**: 179–181.
9. Mushambi MC, Halligan AW, Williamson KW. Recent developements in the pathophysiology and the management of pre-eclampsia. *British Journal of Anaesthesia* 1996; **76**: 133–148.
10. Report on Confidential Enquiries into Maternal Deaths in the UK. Department of Health. London: HMSO, 1988–1990.

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Tolerance of laparoscopy for resection of phaeochromocytoma

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Summary

We describe two patients who underwent resection of phaeochromocytoma by a laparoscopic approach. Although outcome from surgery was successful, there was marked variability in hormonal and haemodynamic changes. In one patient, despite an infusion of nicardipine, peritoneal insufflation produced a marked increase in catecholamine concentrations associated with transient but intense vasoconstriction, but there was no change in the second patient. In both patients, exsufflation caused no significant haemodynamic changes in spite of the high doses of nicardipine given throughout the procedures. (*Br. J. Anaesth.* 1996; **77**: 795–797)

Key words
Surgery, laparoscopy. Complications, phaeochromocytoma. Carbon dioxide, pneumoperitoneum.

Surgical removal of phaeochromocytoma is a risky procedure because of preoperative cardiovascular changes, particularly during surgical manoeuvres. Preoperative preparation, completed during operation by administration of antihypertensive agents, enables the anaesthetist to largely control the haemodynamic instability.[1–3] However, acute complications may still occur.[2 4] The laparoscopic approach described recently seems to be of great interest as it may decrease postoperative morbidity and it allows viewing of the whole of the abdominal cavity in order to reveal possible multiple tumour sites.[5 6] Nevertheless, as the pneumoperitoneum may induce haemodynamic disturbances,[7] the safety of this technique remains questionable. We report two cases in which we measured the haemodynamic changes induced by pneumoperitoneum during removal of phaeochromocytoma by a laparoscopic approach.

Case reports

PATIENT NO. 1

A 32-yr-old woman (50 kg, 158 cm) was referred with a phaeochromocytoma of the right adrenal gland, manifest clinically as hypertension, sweating and severe headache. Urinary catecholamine concentrations were 34 300 nmol/24 h (normal values 150–1600 nmol). Echocardiography revealed left ventricular hypertrophy with a wall thickness of 17 mm. Systolic arterial pressure (SAP), recorded continuously, averaged 165 mm Hg with peaks of 240 mm Hg. Continuous ECG showed several episodes of supraventricular arrhythmia. Treatment with nicardipine 150 mg day^{-1} and labetalol 200 mg day^{-1} for 10 days did not provide satisfactory haemodynamic control.

One hour before surgery and after oral premedication with hydroxyzine 100 mg and alprazolam 0.5 mg, SAP was 202 mm Hg and heart rate 109 beat min^{-1}. Anaesthesia was induced with fentanyl 0.5 mg, midazolam 15 mg and vecuronium 6 mg, and maintained with an infusion of fentanyl 1 mg h^{-1}, midazolam 10 mg h^{-1} and additional bolus doses of vecuronium. No inhalation agents were used and patient's lungs were ventilated mechanically with 60% nitrogen in oxygen at a rate of 15 bpm with a tidal volume of 8–10 ml kg^{-1}, maintaining end-expired carbon dioxide concentration at 3.5–4%. After a bolus of 2 mg, an infusion of nicardipine 4 mg h^{-1} was given to maintain SAP at 140–150 mm Hg.

A pulmonary artery catheter was inserted for continuous measurement of cardiac output (Intellicath 8F-Catheter and Vigilance Monitor, Baxter, USA); additional monitoring included invasive measurement of arterial pressure, pulse oximetry, capnography and ECG. Blood sampling was hourly, performed to measure blood-gas tensions. Plasma concentrations of catecholamines were measured using high-pressure liquid chromatography (table 1). Normovolaemic haemodilution of 600 ml was undertaken using hydroxyethyl starch and 2000 ml were given to produce a pulmonary capillary wedge pressure of 18 mm Hg. After this 90-min preparation phase, the patient was placed in a left lateral decubitus position of 30°. A carbon dioxide pneumoperitoneum with a pressure of 10 mm Hg was produced for 10 min and then suddenly, a hypertensive peak (244/131 mm Hg) with a reduction in heart rate was observed, but without any variation in cardiac output (fig. 1). This episode was controlled rapidly with nicardipine 5 mg i.v. followed by an infusion of 6 mg h^{-1}.

The various vascular tumour pedicles were isolated successively using four trocars. Despite continuous administration of nicardipine, vascular

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Table 1 Variations in plasma concentration of noradrenaline/adrenaline (nmol litre^{-1}) immediately before insufflation of the pneumoperitoneum (prePNP), 5 min (PNP), 1 h (PNP+1), 3 h (PNP+3) and 4h (PNP+4) after insufflation of the pneumoperitoneum, and 30 min after exsufflation (postPNP). (Normal values: noradrenaline < 4 nmol litre^{-1}; adrenaline < 1 nmol litre^{-1}. Dopamine concentrations were normal

	PrePNP	PNP	PNP+1	PNP+3	PNP+4	PostPNP
Patient No. 1	22/2	79/3.2	57/3.6	154/9.8	8/2.3	107/3.3
Patient No. 2.	12/1.1	8.7/1.2	10.4/1.3	36/7.6	4.9/5.1	9.1/1.4

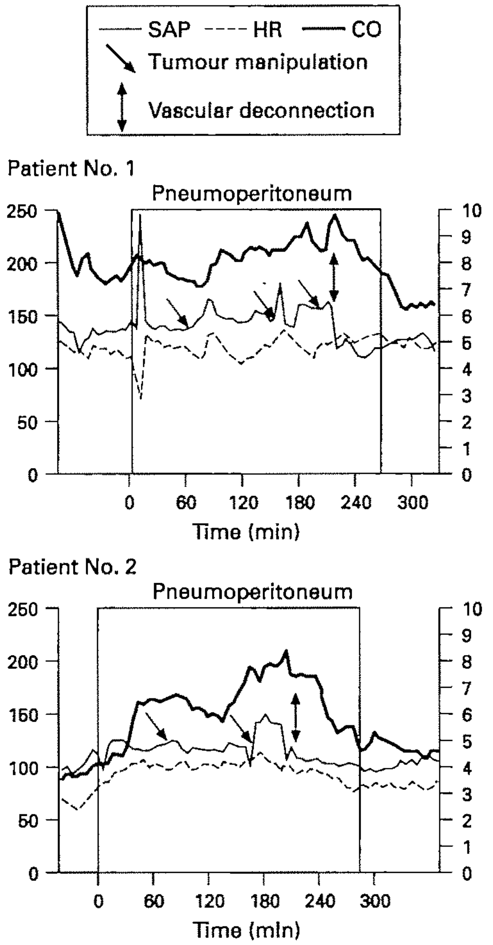

Figure 1 Time course of changes in systolic arterial pressure (SAP), heart rate (HR) and cardiac output (CO) during pneumoperitoneum and surgical procedures in the two patients.

clamping near the tumour caused marked haemodynamic changes. Supplementary bolus doses of nicardipine and bolus doses of esmolol were given when tachycardia or an increase in cardiac output, or both, were observed. After total vascular detachment of the tumour (fig. 1: double arrow), nicardipine was stopped. The tumour (6 cm in diameter) was then extracted via a MacBurney incision. The total preoperative doses of nicardipine and esmolol were 96 and 170 mg, respectively. At the end of the procedure, core body temperature was 36.2 °C. Throughout the operation, Pa_{CO_2} had been maintained at 4.1–4.9 kPa. The postoperative course was uneventful and antihypertensive treatment was not required. Analgesia comprised non-steroidal anti-inflammatory analgesics only. The patient's trachea was extubated 6 h later in the recovery room and she was transferred to the surgical unit. Oral feeding was resumed at 24 h and the patient was discharged on the third day after operation.

PATIENT NO. 2

A 64-yr-old woman (54 kg, 147 cm) was referred with a phaeochromocytoma of the left adrenal gland. The clinical picture comprised arterial hypertension, sweating, palpitations and Raynaud's phenomenon. Urinary concentrations of catecholamines were 13200 nmol/24 h (normal values 150–1600 nmol). Echocardiography revealed left ventricular hypertrophy with a wall thickness of 19 mm with moderate aortic stenosis. Treatment with nicardipine 100 mg day^{-1} for 20 days stabilized arterial pressure.

One hour before surgery and after oral premedication with hydroxyzine 100 mg and alprazolam 0.5 mg, SAP was 141 mm Hg and heart rate 88 beat min^{-1}. Anaesthesia was induced with fentanyl 0.4 mg, midazolam 10 mg and vecuronium 6 mg, and maintained by continuous infusion of fentanyl 0.4 mg h^{-1}, midazolam 4 mg h^{-1} and additional doses of vecuronium. SAP was then stabilized at 90–100 mm Hg without administration of nicardipine. No inhalation agents were used and haemodynamic and ventilatory management, and blood-gas tensions were measured, as described for patient No. 1. Normovolaemic haemodilution of 500 ml was undertaken and 1750 ml were given to produce a pulmonary capillary wedge pressure of 15 mm Hg. The patient was then placed in a right lateral decubitus position of 30°. A bolus of nicardipine 1.5 mg was administered, followed by an infusion of 6 mg h^{-1}. Haemodynamic disturbances caused by tumour manipulation were treated in the same way as those described for patient No. 1. The total peroperative doses of nicardipine and esmolol were 36 and 150 mg, respectively. At the end of the procedure, core body temperature was 35.9 °C. Throughout the operation, Pa_{CO_2} had been maintained at 3.9–4.4 kPa. The postoperative course was uneventful and antihypertensive treatment was not required. Analgesia comprised non-steroidal anti-inflammatory analgesics only. The patient's trachea was extubated 4 h later in the recovery room and she was transferred to the surgical unit. Oral feeding was resumed at 24 h and the patient was discharged on day 4 after operation.

Discussion

The cardiovascular changes induced by phaeochromocytoma are usually aggravated by the stress of surgery. Classically, arterial hypertension occurs, caused by intense vasoconstriction, often associated with myocardial hyperexcitability and arrhythmias.[24] Adrenalectomy using a laparoscopic approach has been proposed with the aim of diminishing the stress of laparotomy and avoiding direct manipulation of the gland.[5,6] However, creation of a pneumoperitoneum by carbon dioxide insufflation carries problems as it causes an increase in intra-abdominal pressure and leads to absorption of carbon dioxide.[7,8] The increase in intra-abdominal pressure causes a decrease in cardiac index by reduction of venous return and an increase in peripheral vascular resistance.[8,9] Excessive absorption of carbon dioxide may lead to sympathetic stimulation with, in extreme cases, arrhythmias induced by hypercapnia.[10] Therefore, the use of laparoscopy for phaeochromocytoma is only justifiable if it is possible to rigorously control preload, afterload and arterial $P\mathrm{CO}_2$. Our experience in the anaesthetic management of laparoscopy has led us to use calcium-channel blockers to control vasoconstriction associated with pneumoperitoneum. Moreover, with hyperventilation, hypercapnia is generally avoided. The anaesthetic technique used here did not differ from that used for conventional phaeochromocytoma surgery. The use of a potent analgesic at a high dose and a benzodiazepine proved to be sufficient to control surgical stress.[11] Calcium-channel blockers, such as nicardipine, are currently the antihypertensive agent of choice during phaechromocytoma resection.[1,11]

Meurisse and colleagues[6] observed good haemodynamic stability during laparoscopic removal of phaeochromocytoma. However, these authors admitted that insufflation of the pneumoperitoneum was a critical time. In this study, although the conditions for pneumoperitoneum were exactly the same, the responses observed in the two patients were not comparable. In our first patient, after insufflation, noradrenaline concentrations increased to three times pre-insufflation concentrations, which was probably an indication of intense mechanical stimulation of the tumour by intra-abdominal pressure. Despite preliminary infusion of nicardipine, the immediate consequence was intense vasoconstriction with a marked increase in arterial pressure. This hypertensive bout was nevertheless controlled rapidly by an additional bolus of nicardipine. In spite of the lower doses of nicardipine in our second patient, there was no vasopressor response to the pneumoperitoneum and no variation in catecholamine concentrations was recorded. In contrast, in both patients, insufflation of the pneumoperitoneum had no effect on cardiac output, whereas a 15–20% reduction in cardiac index is usually observed during conventional laparoscopic surgery.[8] The explanation for the stability was probably the preload optimization by monitoring of pulmonary capillary wedge pressure.[11,12] Recently, Giebler and colleagues performed phaeochromocytoma resection using a capnoretroperitoneoscopic technique.[13] Although they were not reported in detail, the haemodynamic changes seem to have been well tolerated.

Tumour manipulation causes marked increases in arterial pressure, heart rate and cardiac output. Administration of nicardipine or esmolol, or both, makes it possible to maintain satisfactory haemodynamic stability. However, considerable release of noradrenaline was observed in patient No. 1. In common with insufflation, successive laparoscopic manipulation may lead to significant tumour stimulation. Total tumour removal leads to a rapid decrease in catecholamine concentrations with a parallel decrease in cardiac output and vascular resistances. However, in both patients, exsufflation caused no significant haemodynamic changes in spite of the large doses of nicardipine.

References

1. Arai T, Hatano Y, Ishida H, Mori K. Use of nicardipine in the anesthetic management of pheochromocytoma. *Anesthesia and Analgesia* 1986; **65**: 706–708.
2. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *British Journal of Anaesthesia* 1986; **58**: 1453–1568.
3. Nicholas E, Deutschman CS, Allo M, Rock P. Use of esmolol in the operative management of pheochromocytoma. *Anesthesia and Analgesia* 1988; **67**: 1114–1117.
4. Desmonts JM, Marty J. Anaesthetic management of patients with phaeochromocytoma. *British Journal of Anaesthesia* 1984; **56**: 781–789.
5. Gagner M, Lacroix A, Bolté E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *New England Journal of Medecine* 1992; **327**: 1033.
6. Meurisse M, Joris J, Hamoir E, Hubert B, Charlier C. Laparoscopic removal of pheochromocytoma, Why? When? and Who? (Reflexion on one case report). *Surgical Endoscopy* 1995; **9**: 431–436.
7. Kashtan J, Green JF, Parsons EQ, Holcrotft JW. Hemodynamic effects of increased abdominal pressure. *Journal of Surgical Research* 1981; **30**: 249–255.
8. Joris J, Noirot D, Legrand M. Hemodynamic changes during laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1993; **76**: 1067–1071.
9. O'Leary E, Hubbard K, Tormey W, Cunningham AJ. Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. *British Journal of Anaesthesia* 1996; **76**: 640–644.
10. Lenz RJ, Thomas TA, Wilkins DG. Cardiovascular changes during laparoscopy. *Anaesthesia* 1976; **31**: 4–12.
11. Colson P, Ribstein J. Stratégie simplifiée pour l'anesthésie du phéochromocytome. *Annales Françaises d'Anesthésie et de Réanimation* 1991; **10**: 456–462.
12. Mihm FG. Pulmonary artery pressure monitoring in patients with pheochromocytoma. *Anesthesia and Analgesia* 1983; **62**: 1129–1133.
13. Giebler RM, Walz MK, Peitgen K, Scherer RU. Hemodynamic changes after retroperitoneal CO_2 insufflation for posterior retroperitoneoscopic adrenalectomy. *Anesthesia and Analgesia* 1996; **82**: 827–831.

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COMMENTARIES

Randomization is important in studies with pain outcomes: systematic review of transcutaneous electrical nerve stimulation in acute postoperative pain

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Summary

We set out to examine the evidence for the importance of randomization of transcutaneous electrical nerve stimulation (TENS) in acute postoperative pain. Controlled studies were sought; randomization and analgesic and adverse effect outcomes were summarized. Forty-six reports were identified by searching strategies. Seventeen reports with 786 patients could be regarded unequivocally as randomized controlled trials (RCT) in acute postoperative pain. No meta-analysis was possible. In 15 of 17 RCT, we judged there to be no benefit of TENS compared with placebo. Of the 29 excluded trials, 19 had pain outcomes but were not RCT; in 17 of these 19 TENS studies, the authors concluded that TENS had a positive analgesic effect. No adverse effects were reported. Non-randomized studies overestimated treatment effects. (*Br. J. Anaesth.* 1996; **77**: 798–803)

Key words

Anaesthesia, audit. Pain, postoperative. Nerve, stimulation.

Transcutaneous electrical nerve stimulation (TENS) was developed originally as a means of controlling pain through the "gate" theory.[1] There is conflicting professional opinion on the use of TENS in acute postoperative pain. The recommendations of the Agency for Health Care Policy and Research (AHCPR)[2] for acute pain management state that TENS is "effective in reducing pain and improving physical function" while the earlier report of the UK College of Anaesthetists' working party on pain after surgery[3] states that "TENS is not effective as the sole treatment of moderate or severe pain after surgery". For postoperative pain some textbooks recommend or strongly recommend TENS,[4–8] although one at least is uncertain.[9] TENS is of doubtful benefit in labour pain,[10] but we could find no systematic review of its use in chronic pain.

The quality of methods used in clinical studies has been shown to be a key determinant of the eventual results. Schulz and colleagues[11] demonstrated that studies that were not randomized or which were inadequately randomized exaggerated the estimate of treatment effect by up to 40%. Studies which are not fully blinded can exaggerate the estimate of treatment effect by up to 17%. We sought evidence of the effect of randomization in trials with pain as an outcome, in studies of TENS in acute postoperative pain.

Methods

Several different search strategies were used to identify controlled studies for TENS in acute postoperative pain in both MEDLINE (1966–1995: Knowledge Server version 3.25: January 1996) and the Oxford Pain Relief Database (1950–1992).[12] The words "TENS" and "transcutaneous electrical nerve stimulation" were used in searching, including combinations of these words. Additional reports were identified from the reference lists of retrieved reports, review articles and textbooks.

Inclusion criteria were full journal publication, TENS and postoperative pain with pain outcomes. Reports of TENS for the relief of other acute pain conditions, such as labour pain, acute infections and procedures, or those where the number of patients per treatment group was fewer than 10 were excluded. Abstracts and review articles were not considered. Unpublished reports were not sought. Neither authors of reports nor manufacturers of TENS equipment were contacted.

Two types of control predominated—open studies compared TENS with conventional postoperative analgesia (i.m. opioid) or with disabled TENS instruments (sham TENS). Some studies used blinded observers. While there was no prior hypothesis that TENS could not be blinded adequately, it was determined that, despite the considerable efforts documented in some reports, adequate blinding was impossible in practice.

Each report which could possibly meet the inclusion criteria was read by each author independently and scored for inclusion and quality using a three-item scale.[13] Included reports received one point for randomization, a further point if this had been done correctly and a third if the number and

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reasons for withdrawals were given. Authors met to agree that studies were randomized or if the description of the method of randomization was adequate.[11]

Information on surgery, number of patients, study design and duration of treatment was extracted from randomized reports. The type of TENS equipment, its settings and the method and frequency of its use, and placement of electrodes were also extracted. Control group design and the use of TENS in these controls were similarly noted. Pain outcomes, overall findings and conclusions were noted for each report, together with adverse effect information.

A judgement was then made by us as to whether the overall conclusion of the randomized reports was positive or negative for the analgesic effectiveness of TENS. *Post hoc* subgroup analysis in the original reports was not considered in our judgement of overall effectiveness. Reports which had pain measures but which were not randomized or were inadequately randomized were examined for positive or negative analgesic effectiveness of TENS using the judgement of their authors.

Results

Forty-six reports were considered; three did not have pain outcomes, three had fewer than 10 patients per group, three had methodological problems and one reported on pain during rather than after a procedure. These were not considered further.

Nineteen reports were either not RCT or the method of randomization was inappropriate (table 1). Seventeen of the 19 reports with pain measures excluded because they were either not randomized or inadequately randomized, were judged by their authors to have positive analgesic results for TENS in acute postoperative pain.

Seventeen randomized studies with pain outcomes were found. Of these, 15 were judged by us to show no analgesic benefit of TENS in acute postoperative pain.

RANDOMIZED STUDIES

The randomized studies contained information on 786 patients (table 2). TENS was used after various operative procedures, including cardiothoracic, major orthopaedic and gastrointestinal surgery. Ten different TENS machines were used with different control settings and durations of treatment; individual titration of settings took place in six reports. Fourteen reports compared TENS with sham TENS without batteries, with batteries reversed or with sub-threshold stimulation; the other three compared TENS and i.m. opioid with i.m. opioid alone. Quality scores were generally 1 or 2 out of a maximum of 3. The most common outcome measures reported were analgesic consumption and a variety of pain score measurements. Information was not presented in formats which allowed extraction for meta-analysis (table 2).

TENS vs *sham TENS*

Fourteen of the 17 included RCT compared TENS with sham TENS; no differences were found. One of the 14[48] reported no significant difference between TENS and sham TENS for analgesic consumption, but did report a statistically significant difference for pain intensity in favour of the active TENS; the published results, however, used a one-tailed statistical test which we judged inappropriate.

TENS vs *opioid control*

Seven of the 17 included RCT compared opioid plus TENS with opioid alone, four of which also included sham TENS. Of the seven studies, five failed to detect any differences in analgesic consumption or pain measurements between TENS and non-TENS controls. Two reports were judged by their authors and by us to be positive.[42 46]

Pike[42] studied 40 patients after total hip replacement. The study had as its main outcome measure the number of pethidine injections in the first 2 days

Table 1 Non-randomized reports

Reference	Pain condition or operation type	Description	Authors' judgement about analgesic effectiveness
14	Upper abdominal	Not RCT	Positive
15	Cholecystectomy, hernia repair	Retrospective, not RCT	Positive
16	Upper abdominal	Inadequate randomization	Positive
17	Foot	Not RCT — matched case control	Positive
18	Caesarean section	Not RCT	Positive
19	General	Not RCT	Positive
20	Spinal fusion	Not RCT	Positive
21	Foot	Retrospective, not RCT	Positive
22	Urological	Not RCT	Positive
23	Urological	Not RCT	Positive
24	Urological	Not RCT	Positive
25	Abdominal, thoracic	Not RCT	Positive
26	Cholecystectomy	Not RCT	Negative
27	Thoracotomy	Inadequate randomization method	Positive
28	Laparotomy	Retrospective, not RCT	Positive
29	Low back	Not RCT	Positive
30	Lumbar, hip, gynaecological	Retrospective, not RCT	Positive
31	Knee and hip joint	Not RCT	Positive
32	Gastric bypass	Not RCT	Negative

Table 2 Randomized reports

Reference	Operation type	Study design and duration of treatment periods	No. of patients	TENS details	TENS control setting	TENS control	Pain outcomes	Results for pain outcomes	Judgement	Score
33	Appendicectomy	Parallel group TENS (15) Sham TENS (13) Standard postop. analgesia (14) 48 h	42	Dow Corning Wright, single channel, electrodes (either side of wound)	Fixed rate (tingling sensation preop.)	Sham TENS (not turned on)	VASPI @ 48 h, analgesic consumption (24 and 48 h)	No significant difference sham and active TENS for pain and drug consumption; significant difference for pain intensity control *vs* TENS and sham TENS ($P<0.01$)	Negative	1
34	Abdominal	Parallel group Sham TENS (53) TENS (53) 72 h	106	Codman, dual channel, 2 electrodes (either side of wound)	Fixed rate (tingling sensation preop.), rectangular wave form, pulse width (170 ms), pulse rate 80 s^{-1}, output 15 mA	Sham TENS (batteries reversed)	VASPI —average pain twice daily, Pmorphine consumption	No significant differences between TENS and sham TENS	Negative	2
35	Caesarean section	Parallel group (female) GA+TENS (10) Extradural+TENS (11) GA+Sham TENS (8) Extradural+sham TENS (6) 24 h	35	Stim-tec EPC Mini, Model 6011, dual channel (1 channel only used), 2 electrodes (either end of wound)	Amplitude individually titrated, wave fixed (during surgery)	Sham TENS (no batteries)	VASPI—hourly, time to first analgesic, analgesic consumption	No overall difference in analgesic consumption or pain	Negative	2
36	Coronary artery bypass	Parallel group (males) TENS (15) Sham TENS (15) Postop. analgesia (15) 72 h	45	Nuwave, Staodyn. 1 pair electrodes (T1-T5), 1 pair (either side of wound)	Individually titrated (tingling sensation)	Sham TENS (no current)	Pain (0-10) on cough and rest, opioid consumption	No significant differences TENS *vs* sham TENS	Negative	2
37	Cholecystectomy	Parallel group TENS (14) Remote TENS (12) Postop. analgesia (14) 48 h	40	3M Tenzcare, dual channel, site of electrodes not described	Individually titrated	Sham TENS (remote non-segmental)	VASPI, CATPI (4-point) @ 24 and 48 h, analgesic consumption	No significant difference TENS *vs* sham TENS for pain or analgesic consumption. Pain but not analgesic consumption significantly worse in control group ($P<0.05$) immediately after surgery	Negative	1
38	Herniorrhaphy	Parallel group (males) TENS (20) Sham TENS (20) 72 h	40	Dow Corning, Wright Care, dual channel, 2 electrodes (either side of wound)	Individually titrated—pulse duration 180 μs, frequency 70 Hz, amplitude 7.5	Sham TENS (no current)	VASPI twice daily, analgesic consumption	No significant differences TENS *vs* sham TENS	Negative	1
39	Abdominal	Parallel group TENS (15) Sham TENS (15) 48 h	34	Neuromed 3722, 2 electrodes (either side of wound)	Individually titrated (tingling sensation)	Sham TENS (batteries reversed)	VASPI (2, 4, 6, 24, 48 h), analgesic consumption	No significant differences TENS *vs* sham TENS	Negative	2
40	Laminectomy	Parallel group TENS (10) Sham TENS (10) 24 h	20	Dow Corning, Wright Care, dual channel, 4 electrodes (at each end and on either side of wound)	Individually titrated, 180 μs pulsed width, frequency 70 Hz	Sham TENS (no current)	PCA morphine consumption 24 h	No significant differences TENS *vs* sham TENS	Negative	2
41	Cardiac	Parallel group TENS (14) Sham TENS (17) 72 h	31	3M Tenz care Model 6240, dual channel, 2 pairs electrodes (either side of the wound and mid-thoracic region)	Individually titrated—pulse rate 5, width control 3, amplitude	Sham TENS (no batteries)	5 point categorical pain intensity, analgesic consumption	No significant differences TENS and sham TENS	Negative	2
42	Total hip replacement	Parallel group TENS (20) Opioid control (20) 24 h	40	EPC TimeTech clinical stimulator, dual channel, 2 pairs electrodes (1 pr paravertebrally (L2-S2), between trochanter and coccyx, 1 pr above iliac crest, head of fibula)	Individually titrated, continual stimulation		Global assessment, analgesic consumption	Significantly less pethidine consumed in TENS group on day 1 ($P<0.001$)	Positive	1

contd over

26	Cholecystectomy	Parallel group TENS (30) Opioid control (34)	64	EPC, electrodes placed within 2 cm of the wound	Pulse rate 50 s^{-1}, pulsed width 170 ms, amplitude 0–50 A		Daily dose of pethidine for 3 postoperative days	No significant difference	Negative	1
43	Inguinal hernia repair	Parellel group (males) TENS (34) Sham TENS (28) 48 h	62	3M Tenzcare dual channel, 2 pairs of electrodes (over first lumbar vertebra and on either side of wound)	Individually titrated (tingling sensation), 70 Hz rectangular pulse, amplitude	Sham TENS (controls turned off)	VASPI 6, 12, 24, 36, 48 h, opioid consumption	No significant differences TENS *vs* sham TENS	Negative	2
44	Thoracotomy	Parallel group TENS+Omnopon i.m. (20) Omnopon i.m. (20) 48 h	40	Dow Corning, Wright Care 2 channel, 2 electrodes (either side of incision)	Individually titrated, fixed pulse rate 70 s^{-1}, rectangular waveform, pulse width 180 µs		5 point pain intensity 6, 24, 48 h, analgesic consumption, time to oral analgesics, length of hospital stay	No significant differences TENS *vs* sham TENS	Negative	1
45	Abdominal	Parallel group TENS (30) Sham TENS (22) Opioids i.m. (25) 72 h	77	MedGen, electrode placement not described	Fixed—pulse width 80 ms, frequency 40 Hz, amplitude individually titrated	Sham TENS (no current)	Daily 10-point pain intensity	No significant differences TENS *vs* sham TENS, or control	Negative	1
46	Abdominal and thoracic	Parallal group TENS (61) Sham TENS (39) 24 h post surgery until discharge, TDS×20 min	100	Neuromed Model 3700, Meditronic, electrode site individually chosen	Frequency 100–150 s^{-1}, output 20–35, pulse duration 250–400 ms	Sham TENS (no batteries)	Pain, analgesic consumption, duration of relief	Significant difference reported. 2/39 partial relief or complete relief sham TENS *vs* 34/61 with active TENS. Analgesic consumption not reported	Positive	1
47	Total knee replacement	Phase 2—parallel group TENS (18) Sham TENS (18) Postop. analgesia (12) 72 h	48	Strodynamics, continuous. No other information given; electrode placement not described	Amplitude setting individually titrated, pulse duration 100 µs at 70 s^{-1}	Sham TENS (subthreshold stimulation)	Analgesic consumption, hospital stay	No significant differences TENS *vs* sham TENS or control	Negative	1
48	Thoracotomy	Parallel group TENS (12) Sham TENS (12) 48 h	24	3M Tenzcare 6240, 2 electrodes placed on either side of incision	Continuous stimulation, amplitude 7, pulse rate 3, pulse width 5	Sham TENS (no current)	Pain intensity 0–10, analgesic consumption	No significant differences TENS *vs* sham TENS. Positive result reported was with one-tailed test of statistical significance	Negative	2

after operation and a retrospective global rating. Patients with active TENS had significantly fewer pethidine injections on the first day after operation and higher scores on global rating of treatment. VanderArk and McGrath[46] recruited 100 patients undergoing abdominal and thoracic surgery in 2 months, and although there was more success with active TENS used for 20 min three times a day, maximal relief was "almost invariably associated with the first stimulation". Generally there were no obvious differences between the use of TENS in these two positive studies and the 15 which showed no benefit.

Adverse events

No report described systematic recording of adverse events, nor were any reported.

Discussion

The "gold standard" in clinical trials is adequate randomization.[11] Non-randomized studies have been shown for nearly 20 yr to yield larger estimates of treatment effects than studies using random allocation.[49] The degree of exaggeration of treatment effect when randomization is inappropriate can be as much as 40%.[11] These findings underpin the inclusion criteria chosen in systematic reviews.

For TENS in acute postoperative pain, 17 of 19 reports with pain outcomes which were either not randomized or inappropriately randomized claimed TENS to be effective, compared with two of 17 randomized controlled trials.

The possibility of bias exists. The method of randomization was described in only two reports.[16 27] The method described was inadequate in both, one using a nurse to randomize patients[16] and the other using alternate allocation.[27] Reports which said only that they were randomized may have used an inadequate method.

That these data represent the lowest common denominator of information, essentially vote counting rather than a more sophisticated analysis, reflects the nature of the analgesic scoring methods that predominated in the original reports. Pain scoring using analogue or categorical scales was reported as means (an unreliable statistic[50]) or mean analgesic consumption, or time to first analgesic was used. None of these allowed data extraction for further statistical analysis or comparison between reports. While more rigorous pain scoring might have been used, there is no evidence that all of the reports suffered a systematic failure in analgesic measurement.

Inadequacy of blinding in clinical trials of analgesic interventions continues to be of concern,[51] although this may be less of an issue with pharmacological interventions.[50] Blinding of procedures is much more difficult than blinding of drug studies. Most of the TENS studies made attempts at blinding, for example by removing batteries from the TENS apparatus (sham TENS) or by using staff with no knowledge of the study or allocation to conduct the patient assessments. Lack of blinding has been estimated to exaggerate the estimate of treatment effect of studies by some 17%.[11] Adequate blinding of TENS for both carers and patients is particularly difficult.[52] None of the reports was judged to have been blinded and this lowered the quality scores given to the 17 randomized studies. The fact that only two of the reports showed any positive effect of TENS in acute postoperative pain is all the more striking because of this potential overestimation of treatment effect caused by lack of blinding.

The clear message of the reports considered in this systematic review is that adequate randomization is an important quality standard in studies with pain outcomes. Including non-randomized studies in reviews may give the wrong answer. The AHCPR guidelines on acute pain management included non-randomized reports, and this may explain their more positive attitude towards TENS.[2]

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References

1. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150**: 971–978.
2. Acute Pain Management Guideline Panel. Acute pain management: operative or medical procedures and trauma. Clinical Practice Guideline No. 1. Agency for Health Care Policy and Research, US Department of Health and Human Services, eds. *AHCPR Publication No. 92–0032.* Rockville, MD: Public Health Service, Feb 1992: 24–25.
3. *Report of the Working Party on Pain After Surgery.* London: The Royal College of Surgeons of England and the College of Anaesthetists, 1990.
4. Charman RA. Physiotherapy for the relief of pain. In: Carroll D, Bowsher D, eds. *Pain Management and Nursing Care.* Oxford: Butterworth–Heinemann Ltd, 1993; 146–165.
5. Woolf CJ, Thomson JW. Stimulation-induced analgesia: transcutaneous electrical nerve stimulation (TENS) and vibration. In: Wall PD, Melzack R, eds. *Textbook of Pain* 1994; 1191–1217.
6. McCaffery M, Beebe A. *Pain: a Clinical Manual for Nursing Practice.* St Louis: CV Mosby Company, 1989.
7. Chaney ES. The management of postoperative pain. *Pain: Management and Control in Physiotherapy* 1988: 253–268.
8. Park G, Fulton B, eds. *The Management of Acute Pain.* Oxford: Oxford University Press, 1991.
9. Justins DM, Richardson PH. Clinical management of acute pain. *British Medical Bulletin* 1991; 561–583.
10. Carroll D, Tramer T, McQuay H, Nye B, Moore A. Transcutaneous electrical nerve stimulation in labour pain. *British Journal of Obstetrics and Gynaecology* (in press).
11. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. *Journal of the American Medical Association* 1995; 273: 408–412.
12. Jadad AR, McQuay HJ. A high yield strategy to identify randomized controlled trial for systematic reviews. *Online Journal of Current Clinical Trials* 1993; 33:1059–2725.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; **17**: 1–12.
14. Ali J, Yaffe CS, Serrette C. The effect of transcutaneous electric nerve stimulation on postoperative pain and pulmonary function. *Surgery* 1981; **89**: 507–512.
15. Bussey JG, Jackson A. TENS for postsurgical analgesia. *Contemporary Surgery* 1981; **18**: 35–41.
16. Cooperman AM, Hall B, Mikalacki K, Hardy R, Sadar E. Use of transcutaneous electrical stimulation in the control of postoperative pain. *American Journal of Surgery* 1977; **133**: 185–187.
17. Cornell PE, Lopez AL, Malofsky H. Pain reduction with transcutaneous electrical nerve stimulation after foot surgery. *Journal of Foot Surgery* 1984; **23**: 326–333.
18. Hollinger JL. Transcutaneous electrical nerve stimulation after cesarean birth. *Physical Therapy* 1986; **66**: 36–38.
19. Hymes AC, Raab DE, Yonehiro EG, Nelson GD, Printy AL. Electrical surface stimulation for control of acute postoperative pain and prevention of ileus. *Surgical Forum* 1974; **24**: 447–449.
20. Issenman J, Nolan MF, Rowley J, Hobby R. Transcutaneous electrical nerve stimulation for pain control after spinal fusion with Harrington rods. *Physical Therapy* 1985; **65**: 1517–1520.
21. Lanham RH, Powell S, Hendrix BE. Efficacy of hypothermia and transcutaneous electrical nerve stimulation in pediatric surgery. *Journal of Foot Surgery* 1984; **23**: 152–158.
22. Merrill DC. Electroanalgesia in urologic surgery. *Urology* 1987; **29**: 494–497.
23. Merrill DC. FasTENS—a disposable transcutaneous electrical nerve stimulator designed specifically for use in postoperative patients. *Urology* 1988; **31**: 78–79.
24. Merrill DC. Clinical evaluation of FasTENS, an inexpensive, disposable transcutaneous electrical nerve stimulator designed specifically for postoperative electroanalgesia. *Urology* 1989; **33**: 27–30.
25. Neary JM. Transcutaneous electrical nerve stimulation for the relief of post-incisional surgical pain. *American Association Nursing Journal* 1981; **49**: 151–155.
26. Reuss R, Cronen P, Abplanalp L. Transcutaneous electrical nerve stimulation for pain control after cholecystectomy: lack of expected benefits. *Southern Medical Journal* 1988; **81**: 1361–1363.
27. Rooney SM, Jain S, Goldiner PL. Effect of transcutaneous nerve stimulation on postoperative pain after thoracotomy. *Anesthesia and Analgesia* 1983; **62**: 1010–1012.
28. Schomberg FL, Carter-Baker SA. Transcutaneous electrical nerve stimulation for postlaparotomy pain. *Physical Therapy* 1983; **63**: 188–193.
29. Schuster GD, Infante MC. Pain relief after low back surgery: the efficacy of transcutaneous electrical nerve stimulation. *Pain* 1980; **8**: 299–302.
30. Solomon R, Viernstein MC, Long D. Reduction in postoperative pain and narcotic use with transcutaneous electrical nerve stimulation. *Surgery* 1980; **87**: 142–146.
31. Stabile ML, Mallory TH. The management of postoperative pain in total joint replacement. *Orthopaedic Review* 1978; **7**: 121–123.
32. Strayhorn G. Transcutaneous electrical nerve stimulation and postoperative use of narcotic analgesics. *Journal of the National Medical Association* 1983; **75**: 811–816.
33. Conn IG, Marshall AH, Yadav SN, Daly JC, Jaffer M. Transcutaneous electrical nerve stimulation following appendicectomy: the placebo effect. *Annals of the Royal College of Surgeons of England* 1986; **68**: 191–192.
34. Cuschieri RJ, Morran CG, McArdle CS. Transcutaneous electrical stimulation for postoperative pain. *Annals of the Royal College of Surgeons of England* 1985; **67**: 127–129.
35. Davies JR. Ineffective transcutaneous nerve stimulation following epidural anaesthesia. *Anaesthesia* 1982; **37**: 453–457.
36. Forster EL, Kramer JF, Lucy SD, Scudds RA, Novick RJ. Effect of TENS on pain, medications, and pulmonary function following coronary artery bypass graft surgery. *Chest* 1994; **106**: 1343–1348.
37. Galloway DJ, Boyle P, Burns HJ, Davidson PM, George WD. A clinical assessment of electroanalgesia following abdominal operations. *Surgery, Gynecology and Obstetrics* 1984; **159**: 453–456.
38. Gilbert JM, Gledhill T, Law N, George C. Controlled trial of transcutaneous electrical nerve stimulation (TENS) for postoperative pain relief following inguinal herniorrhaphy. *British Journal of Surgery* 1986; **73**: 749–751.
39. Lim AT, Edis G, Kranz H, Mendelson G, Selwood T, Scott DF. Postoperative pain control: contribution of psychological factors and transcutaneous electrical stimulation. *Pain* 1983; **17**: 179–188.
40. McCallum MI, Glynn CJ, Moore RA, Lammer P, Phillips AM. Transcutaneous electrical nerve stimulation in the management of acute postoperative pain. *British Journal of Anaesthesia* 1988; **61**: 308–312.
41. Navarathnam RG, Wang IY, Thomas D, Klineberg PL.

Evaluation of the transcutaneous electrical nerve stimulator for postoperative analgesia following cardiac surgery. *Anaesthesia and Intensive Care* 1984; **12**: 345–350.

42. Pike PM. Transcutaneous electrical stimulation. Its use in the management of postoperative pain. *Anaesthesia* 1978; **33**: 165–171.
43. Smedley F, Taube M, Wastell C. Transcutaneous electrical nerve stimulation for pain relief following inguinal hernia repair: a controlled trial. *European Surgical Research* 1988; **20**: 233–237.
44. Stubbing JF, Jellicoe JA. Transcutaneous electrical nerve stimulation after thoracotomy. Pain relief and peak expiratory flow rate: a trial of transcutaneous electrical nerve stimulation. *Anaesthesia* 1988; **43**: 296–298.
45. Taylor AG, West BA, Simon B, Skelton J, Rowlingson JC. How effective is TENS for acute pain? *American Journal of Nursing* 1983; **83**: 1171–1174.
46. VanderArk GD, McGrath KA. Transcutaneous electrical stimulation in treatment of postoperative pain. *American Journal of Surgery* 1975; **130**: 130–138.
47. Walker RH, Morris BA, Angulo DL, Schneider J, Colwell CW jr. Postoperative use of continuous passive motion, transcutaneous electrical nerve stimulation, and continuous cooling pad following total knee arthroplasty. *Journal of Arthroplasty* 1991; **6**: 151–156.
48. Warfield CA, Stein JM, Frank HA. The effect of transcutaneous electrical nerve stimulation on pain after thoracotomy. *Annals of Thoracic Surgery* 1985; **39**: 462–465.
49. Chalmers TC, Matta RJ, Smith J jr, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *New England Journal of Medicine* 1977; **297**: 1091–1096.
50. McQuay H, Carroll D, Moore A. Variation in the placebo effect in randomised controlled trials of analgesics: All is as blind as it seems. *Pain* 1996; **64**: 331–335.
51. Wall PD. The placebo effect: an unpopular topic. *Pain* 1992; **51**: 1–3.
52. Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. *American Journal of Physical Medicine and Rehabilitation* 1990; **69**: 6–10.

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Guest Reviewers for 1996

Each manuscript submitted to *British Journal of Anaesthesia* is reviewed by members of the editorial staff, and also by individuals with particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaesthesia. Consequently, acceptance for publication is based on the views of two or more individuals as to originality, validity and clinical relevance of the information presented.

The Editor would like to acknowledge the significant contribution made by the undernoted individuals who, in addition to the editorial team, reviewed manuscripts during 1996.

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CORRESPONDENCE

Unexpected high spinal block in obstetrics

Sir,—Elliott, Voyvodic and Brownridge recently reported an unexpected subarachnoid block in a parturient, despite careful aspiration testing and prior administration of local anaesthetic via a catheter, presumably located in the lumbar extradural space.[1] We recently described five similar cases of high spinal block produced by the initial test dose alone after negative aspiration testing.[2] We have had three additional cases since our report, two in labouring parturients and one in an elderly woman undergoing ankle surgery. In common with our previously reported cases, patients were seated during insertion and testing of the catheter, and 18-gauge Tuohy needles with 20-gauge open-tip, single-orifice polyamide catheters were used (B. Braun Medical, Inc., Bethlehem PA, USA). After uneventful catheter insertions, careful negative pressure aspiration produced no fluid. The test dose administered (3 ml of glucose-free 1.5% lignocaine with adrenaline 1:200000) produced abrupt high sensory block and complete lower extremity motor block consistent with subarachnoid injection in each patient. High spinal block was accompanied by profound hypotension in both parturients. One developed a high motor block resulting in ventilatory failure requiring tracheal intubation, followed by emergency Caesarean delivery for persistent fetal bradycardia. In each case, CSF was aspirated easily through the catheter with subsequent negative pressure aspiration testing. As in our previous cases, none of the patients developed postdural puncture headache (PDPH), despite dural and arachnoid punctures.

Several authors have suggested that "a subdural catheter can perforate the arachnoid mater...at any time"[1] and, "the test dose given through a catheter placed in the subdural space causes the arachnoid to tear".[3] We agree, and provide the accompanying figure (fig. 1) as a unified explanation of the mechanisms underlying arachnoid rupture and the associated low incidence of PDPH. Although initial placement of the catheter is subdural, subsequent arachnoid rupture occurs because of sudden positive pressure generated in the low-compliance subdural space by injection of a small volume of fluid. This is consistent with findings common to all our cases, namely absence of CSF during placement of the catheter, inability to aspirate fluid before catheter injection, and free flow of CSF after injection and onset of spinal block. Elliott, Voyvodic and Brownridge did not state if CSF was aspirated after the onset of subarachnoid block, however, computed tomography demonstrated clearly subarachnoid catheter placement in their patient.

Also, consistent with this mechanism is the absence of PDPH in all cases described by us (seven of whom were labouring parturients) and the single parturient described by Palkar, Boudreaux and Mankad.[4] Such a low incidence of PDPH in parturients experiencing arachnoid puncture with an 18-gauge Tuohy needle or 20-gauge extradural catheter is unlikely. However, absence of PDPH might be expected if the dural puncture site and site of arachnoid tear do not overlap, as we propose (fig. 1). After removal of the catheter, positive hydrostatic pressure in the subarachnoid space generated in the upright position should effectively seal the dural hole with underlying arachnoid mater. This contrasts with the more common occurrence of inadvertent dural puncture recognized by immediate CSF flow through the needle or catheter, in which the dural and arachnoid puncture sites directly overlap each other. Such cases have a high risk of PDPH.

Because of the high blocks and hazardous associated effects observed, we have altered our testing of extradural catheters. To help detect a subdural catheter that becomes subarachnoid on injection, we perform a negative pressure aspiration test before and after injection of 3 ml of saline, as suggested by some authors.[5] Injection of 3 ml of saline should be as effective as, and safer than, a local anaesthetic test dose in detecting arachnoid rupture. Furthermore, we have abandoned the lignocaine test dose. Abraham and colleagues proposed hyperbaric 1.5% lignocaine (Xylocaine, Astra, Westboro, MA, USA) as a safe alternative intrathecal marker,[6] however, this incurs significant added expense ($6.65 per 2 ml vial in the USA). Instead, we combine adrenaline 15 μg with 2 ml of glucose-free 0.25% bupivacaine to produce a combined i.v. and intrathecal test solution. Bupivacaine 0.25% (2 ml) has been shown to safely provide rapid onset of labour analgesia and sensory block, with little risk of hypotension or high motor block when administered intrathecally.[7] We find the inclusion of adrenaline useful because of the 5% incidence of i.v. cannulation associated with this catheter in our institution. These changes in both aspiration technique and test dose should minimize the occurrence of unexpected high spinal block without increasing expense or time.

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1. Elliott DW, Voyvodic F, Brownridge P. Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture? *British Journal of Anaesthesia* 1996; 76: 322–324.
2. Richardson MG, Lee AC, Wissler RN. High spinal anesthesia after epidural test dose administration in five obstetric patients. *Regional Anesthesia* 1996; 21: 119– 123.
3. Reynolds F, Speedy HM. The subdural space: the third place to go astray. *Anaesthesia* 1990; 45: 120–123.
4. Palkar NV, Boudreaux RC, Mankad AV. Accidental total

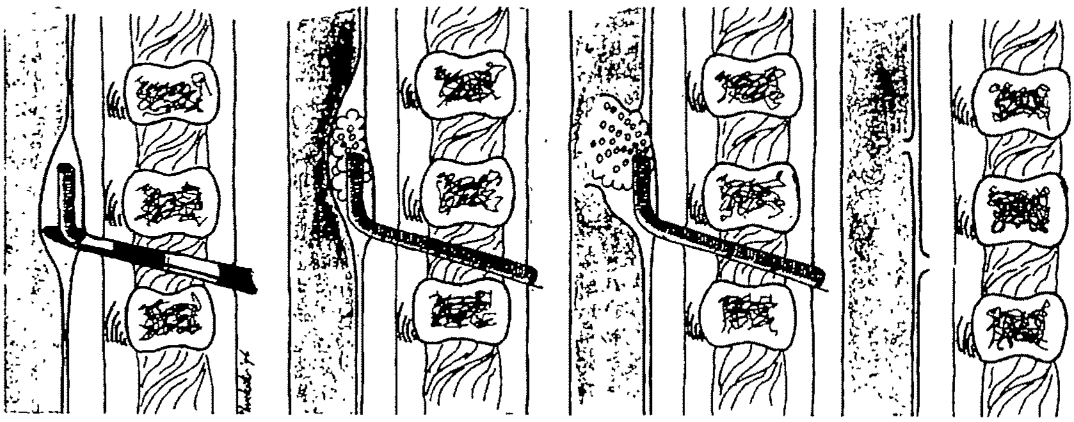

Figure 1 While initial placement of the catheter is subdural, injection of fluid results in disruption of the arachnoid mater. After removal of the catheter, non-adjacent dural and arachnoid defects create a flap valve minimizing CSF leak.

spinal block: a complication of an epidural test dose. *Canadian Journal of Anaesthesia* 1992; 39: 1058–1060.

5. Brown DL. Spinal, epidural, and caudal anesthesia: anatomy, physiology, and technique. In: Chestnut DH, ed. *Obstetric Anesthesia: Principles and Practice.* St Louis: Mosby Yearbook, 1994; 181–201.
6. Abraham RA, Harris AP, Maxwell LG, Kaplow S. The efficacy of 1.5% lidocaine with 7.5% dextrose and epinephrine as an epidural test dose for obstetrics. *Anesthesiology* 1986; **64**: 116–119.
7. Stacey RGW, Watt S, Kadim MY, Morgan BM. Single space combined spinal–extradural technique for analgesia in labour. *British Journal of Anaesthesia* 1993; 71: 499–502.

Is Doppler monitoring mandatory in laparoscopic surgery?

Sir,—In the article published recently by Nyarwaya and colleagues[1] on carbon dioxide embolism in piglets, the authors observed some disturbances in $P\text{E}'_{CO_2}$ and Sp_{O_2}, with few changes in haemodynamic variables, and they concluded that "The presence of Doppler monitoring should be mandatory" in laparoscopic surgery because of the risk of carbon dioxide embolism which may not be detected with usual monitoring (ECG, AP, Sp_{O_2}, $P\text{E}'_{CO_2}$).

Although it is true that carbon dioxide embolism is infrequent during laparoscopic surgery,[2] most occur without any clinical disturbances and are detected only by transoesophageal echocardiography or precordial Doppler,[3] without the need for therapy. For these reasons, in common with other authors,[4] we believe that monitoring of patients without previous pathology should include ECG, AP, $P\text{E}'_{CO_2}$ and Sp_{O_2}. Doppler monitoring, pulmonary catheter, or both, is recommended in patients at risk, although the indications for laparoscopic surgery should be assessed carefully and attention paid to the important haemodynamic changes that occur with pneumoperitoneum.[5 6]

Finally, although carbon dioxide embolism occurs infrequently in laparoscopic surgery, the presence of a patent foramen ovale must be excluded because of the danger of paradoxical embolism.[7 8]

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1. Nyarwaya JB, Pierre S, Mazoit JX, Umbrain V, Romain M, Sammii K, d'Hollander A. Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets. *British Journal of Anaesthesia* 1996; **76**: 428–434.
2. Derouin M, Couture P, Boudreault D, Girard D, Gravel D. Detection of gas embolism by transesophageal echocardiography during laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1996; **82**: 119–124.
3. Delafosse B, Cottin V, Motin J. Embolie gazeuse en chirurgie coelioscopique: monitorage et prevention. Editions Techniques. Encycl Med Chir; Anesthesie-Reanimation, F.A. 36-568-A10,1994.
4. Ananthanarayan C, Paek W, Rolbin SH, Dhanidina K. Hysteroscopy and anaesthesia. *Canadian Journal of Anaesthesia* 1996; 43: 56–64.
5. Portera C, Compton R, Walters D. Benefits of pulmonary artery catheter and transesophageal echocardiographic monitoring in laparoscopic cholecystectomy patients with cardiac disease. *American Journal of Surgery* 1995; **169**: 202–207.
6. Westerband A, Van De Water J, Amzallag M, Lebowitz PW. Cardiovascular changes during laparoscopic cholecystectomy. *Surgery, Gynecology and Obstetrics* 1992; 175: 535–538.
7. Gronert GA, Messick JM, Cucchiara RF, Michenfelder JD. Paradoxical air embolism from a patient foramen ovale. *Anesthesiology* 1979; **50**: 548–549.
8. Failure of preoperative echo testing to prevent paradoxical air embolism: report of two cases. *Anesthesiology* 1989; **71**: 604–607.

Sir,—The letter of Ferrando and colleagues emphasizes at least two important points concerning the risk of gas embolism in anaesthetized patients undergoing laparoscopic surgery. First, they suggest assessing, before operation, in any patient undergoing laparoscopic surgery, whether or not a patent foramen ovale exists. We agree totally with this proposal because of the potential occurrence of venous gas embolism, and subsequent risk of "paradoxical" systemic embolism. Nevertheless, the value of such a preoperative testing procedure will never reach a safety level of 100%.[1] Second, as reported previously[2] (and supported also more recently experimentally[3]), signs of mild carbon dioxide embolism may be difficult to detect if routine monitoring is restricted to ECG, NIBP, Sp_{O_2} and $P\text{E}'_{CO_2}$. For a fixed or even progressively increasing carbon dioxide embolism, the value of $P\text{E}'_{CO_2}$ monitoring for quantification of the magnitude of the carbon dioxide embolism is highly questionable (see fig. 5, upper trace[3]). In any circumstances, carbon dioxide as any other gas embolism is easily detected by more sensitive and specific diagnostic tools, such as pre-thoracic or oesophageal echocardiography.[2 4] For our group, it is not appropriate to expose the patient to the clearly increased risk of gas embolism of changing composition,[5] despite the fact that the nature of the injected gas is obviously carbon dioxide at the start, without having specific and sensitive monitoring for early detection of such events.

In the case of gas embolism with peritoneal carbon dioxide insufflation, the difference between a catastrophe[6 7] and an incident may be the promptness of correct diagnosis obtained with sensitive and specific monitors[4] followed by rapid adequate corrective manoeuvres. For these reasons, we believe that Doppler monitoring is mandatory in laparoscopic surgery.

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1. Cucchiara RF, Nishimura RA, Black S. Failure of preoperative testing to prevent paradoxical air embolism: Report of two cases. *Anesthesiology* 1989; 71: 604–607.
2. Derouin M, Couture P, Boudreault D, Cirard D, Garvel D. Detection of gas embolism by transoesophageal echocardiography during laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1996; 82: 119–124.
3. Nyarwaya J-B, Pierre S, Mazoit J-X, Umbrain V, Romain M, Samii K, d'Hollander A. Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets. *British Journal of Anaesthesia* 1996; **76**: 428–434.
4. Couture P, Boudreault D, Derouin M. Venous carbon dioxide embolism in pigs: an evaluation of end-tidal carbon dioxide, transoesophageal echocardiography, pulmonary artery pressure, and precordial auscultation as monitoring modalities. *Anesthesia and Analgesia* 1994; **79**: 867–873.
5. Diemunsch P, Van Dorsselaer T, Mutter D, Diemunsch A-M, Teller G. Evolution of the nitrous oxide fraction in the carbon dioxide pneumo-peritoneum during laparoscopy under general anesthesia. *Anesthesiology* 1995; **83**: A-1085.
6. Crozier TA, Luger A, Dravecz M. Carbon dioxide embolism with cardiac arrest during hysteroscopy: report on three cases (German). *Anasthesiologica Intensivemed Notfallmed Schmerzther* 1991; **26**: 412–415.
7. Root B, Levy MN, Pollack S, Lubert M, Pathak K. Gas embolism death after laparoscopy by "trapping" in portal circulation. *Anesthesia and Analgesia* 1978; **57**: 232–237.

Fuzzy logic control of inspired volatile anaesthetic concentrations

Sir,—The article of Curatolo and colleagues on fuzzy logic control of inspired isoflurane and oxygen concentrations is in our opinion an important contribution to automatic control of the gaseous composition in the circle system. This seems to be the method of the future to facilitate minimal flow techniques to the majority of anaesthetists. Automatic control, however, should be capable of competing with manually controlled methods.

Our concerns are about the method in which the volatile anaesthetic delivery was calculated. The formula used by the authors seems to take the volatile anaesthetic as a fraction of the fresh gas passing the flowmeters. However, the volatile anaesthetic is added to that gas flow so that total gas flow (100%) consists of the volatile anaesthetic, as set at the vaporizer (vap%), in addition to the fresh gas passing the flowmeters (100%−vap%). Thus volatile delivery has to be calculated as follows:[1]

$$\text{delivery} = \frac{\text{EGF}}{1 - \frac{\text{Vap}}{100}} - \text{FGF (ml min}^{-1}\text{)}$$

where FGF=sum of fresh gas set at the flowmeters (ml min^{-1}) and Vap=vaporizer setting (vol%).

Comparison of the results from the two formulae shows that volatile delivery calculated by the formula used in this article is underestimated to a percentage corresponding to the vaporizer setting (vap%).[2] While 1–5 % may be negligible for traditional volatile agents and when only costs are of concern, the difference becomes relevant with volatile agents used in high concentrations, such as desflurane, and in relevant studies, such as the one considered here. The article compared a "low flow" and a "minimal flow" technique. During minimal flow, the vaporizer is at higher settings than during low flow. Consequently, underestimation of volatile consumption is more pronounced in the minimal flow group than in the low flow group. Thus the data given in the article show a slightly greater difference in delivery between the two groups than is actually there.

Compared with our own experience, volatile anaesthetic consumption reported in this study with respect to only the maintenance period appears to be high. In manually controlled minimal flow techniques we calculated an average isoflurane delivery of only 12.9 ml min^{-1} in 20 entire anaesthetics for the period from intubation to extubation (thus including the wash-in periods) lasting 149±69 min maintained at an end-tidal isoflurane concentration of approximately 0.8 vol%.[3] We used an Ohmeda Modulus CD/CV with the MAS circle system, the volume of which is approximately 1.5 litre less than that of the Dräger Cicero used by Curatolo and co-workers.

The frequent sharp increases in fresh gas flow to remove foreign gas from the circle system are quoted to explain why the net difference in volatile consumption between the two flow rates is relatively small. One may consider that the higher volume of the circle system makes the excess gas during minimal flow and the high flow flush less effective in removing foreign gases from the circle system. Furthermore, the system response to changes in the vaporizer setting are slower with a larger circle system. These factors may have contributed to the lower volatile anaesthetic consumption in our work.

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1. Curatolo M, Derighetti M, Petersen-Felix S, Feigenwinter P, Fischer M, Zbinden AM. Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia. *British Journal of Anaesthesia* 1996; 76: 245–250.
2. Kuhn I, Wissing H, Vetterman J. Ein neues Arbeitsblatt zur Berechnung von Narkosekosten-Validierung der Berechnungsverfahren über den Verbrauch volatiler Anästhetika. *Anästhesie Intensivmedizin* 1995; 36: 242–248.
3. Kuhn I, Wissing H. Wirtschaftlichkeit von Desfluran im Vergleich zu Isofluran bei Niedrigflußnarkosen. *Anaesthesist* 1995; 44: S459.

Sir,—We thank Drs Wissing and Kuhn for their interest in our investigation and for their comments.

We agree that the formula to calculate isoflurane delivery suggested by Drs Wissing and Kuhn gives a more precise estimation. However, as they pointed out, underestimation resulting from our formula is quantitatively insignificant and does not therefore influence the conclusions of the investigation. We agree that a more accurate calculation should be used when performing a similar study on desflurane.

Concerning the difference in isoflurane consumption between our study and the experience of Drs Wissing and Kuhn, we believe that such a comparison cannot be made without more detailed information on patients characteristics, premedication, co-administration of other analgesics, anaesthetist involved, surgical procedures, etc. All of these factors can greatly affect isoflurane delivery. Furthermore, median fresh gas flow in our study was higher than 0.5 litre min^{-1} (table 5) because of the occasional activation of the "turbo" mode (fresh gas flow 10 litre min^{-1}) when a rapid change in the inspired isoflurane concentration was desired.

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Hypotension during subarachnoid anaesthesia

Sir,—The article by Drs Critchley and Conway[1] investigating the effects of colloid or metaraminol, or both, in patients receiving subarachnoid anaesthesia to facilitate surgery for fractured neck of femur makes interesting reading. However, I should like to make two comments, particularly concerning their conclusion that "hypotension may be treated more effectively by using a vasopressor".

First, elderly patients presenting for fractured neck of femur surgery are, in my experience, almost invariably hypovolaemic, through loss of considerable blood volume into the fracture site and also through inadequate fluid intake in the orthopaedic wards. Performing subarachnoid block in hypovolaemic patients is dangerous[2] and therefore I believe that correction of hypovolaemia is of paramount importance in this group of patients before the use of any vasoconstrictor therapy. The statistically significant increases in mean cardiac index and central venous pressure reported in the colloid only group may represent adequate fluid replacement.

Second, we do not know if the use of metaraminol is without risk, particularly when used as an infusion in these elderly patients with potential widespread atherosclerosis. Is the routine use of a vasoconstrictor in the treatment of modest hypotension of any improved *long-term* benefit to the patient compared with fluid replacement therapy? While I accept that this was a physiological study examining the short-term effects of colloid and metaraminol, I do not believe that one can draw conclusions on which is the better treatment of hypotension without examining the incidences of postoperative complications.

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1. Critchley LA, Conway F. Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol. *British Journal of Anaesthesia* 1996; 76: 734–736.
2. Kennedy WF jr, Bonica JJ, Akamatsu TJ, Ward RJ, Martin WE, Grinstein A. Cardiovascular and respiratory effects of subarachnoid block in the presence of acute blood loss. *Anesthesiology* 1968; 29: 29–35.

Sir,—Thank you for the opportunity to reply to Dr Watters' letter commenting on our recent article on the use of colloids and metaraminol during spinal anaesthesia in patients with femoral neck fractures.[1]

Normovolaemia is essential before spinal anaesthesia. It is therefore standard practice in our hospital that all patients admitted with femoral neck fractures have i.v. hydration on admission to compensate for blood loss at the fracture site and fasting. Despite this practice, patients with femoral neck fractures still experience a greater decrease in arterial pressure during spinal anaesthesia compared with other groups, such as urology patients.[2] We believe that this increase in hypotension is caused by vasodilatation of blood vessels that become abnormally vasoconstricted as a result of the pain and trauma associated with the fracture site.

In our study we measured the effects of treatment with colloid and metaraminol on preload during spinal block. We found that both colloid 8 ml kg^{-1} and metaraminol by i.v. infusion were equally effective in correcting decreases in preload. However, the use of larger volumes of i.v. fluids to prevent hypotension has repeatedly been shown to be ineffective.[3–5] Thus vasopressors are commonly advocated. Although we cannot comment on the long-term effects of using metaraminol, we did limit our dose to the minimum required to maintain normal arterial pressure and by using an infusion we avoided excessive swings in arterial pressure.

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1. Critchley LAH, Conway F. Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid *vs* metaraminol. *British Journal of Anaesthesia* 1996; **76**: 734–736.
2. Critchley LAH, Stuart CJ, Short TG, Gin T. Haemodynamic effects of subarachnoid block in elderly patients. *British Journal of Anaesthesia* 1994; **73**: 464–470.
3. Ceo AJ, Revanas B. Is crystalloid preloading useful in spinal anaesthesia in the elderly? *Anaesthesia* 1990; **45**: 241–243.
4. Critchley LAH, Short TG, Gin T. Hypotension during subarachnoid anaesthesia: a haemodynamic analysis of three treatments. *British Journal of Anaesthesia* 1994; **72**: 151–155.
5. Rocke DA, Rout CC. Volume preloading, spinal hypotension and Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 257–259.

Haemodilution induces a hypercoagulable state

Sir,—We read with interest the article by Ruttmann, James and Viljoen on hypercoagulability induced by 20% dilution of whole blood with isotonic saline or gelatine.[1] In this study, coagulation was measured using native thrombelastography (TEG), and a shortening of *r* and *k* times, and an increase in MA were found. We would like to report our own observations.

In a similar investigation involving 12 volunteers, 10 ml of citrated blood were obtained and native TEG was performed with undiluted blood (control) and with a 20% *in vitro* dilution using 0.9% saline. The volunteers then received 1 litre of the same saline solution i.v. (equal to a 20% dilution) and another TEG measurement was performed. Our results are shown in table 1.

These data confirm the results of Ruttmann, James and Viljoen showing a hypercoagulable state when saline was mixed *in vitro*. However, after i.v. infusion of saline, no significant changes in TEG variables were observed. Thus we suggest that the reported effect might be an *in vitro* phenomenon. Our opinion is enforced by observations using activated TEG (activation with Innovin 5 μl) which revealed no significant changes when saline was added *in vitro*.[2] This indicates that the *in vitro* effect might be a pitfall of native thrombelastography.

There are no data to explain this phenomenon. Non-activated (native) thrombelastography is a very sensitive method for evaluating factors influencing coagulation. This is seen for example in the long *r* time of the control in this study (9 min). Conclusions based on the effects seen in non-activated thrombelastographic measurements to the *in vivo* situation should be drawn with great care as the activation situation in non-activated thrombelastographic measurements does not reflect the *in vivo* situation. In the body, coagulation takes place mainly after severe extrinsic activation, for example after vascular injury.

The low contact activation of the coagulation system in native TEG measurements is not a physiological situation. With respect to the better clot formation and higher MA in the *in vitro* saline tests compared with the control, the following mechanism should be excluded: it is known that a high sedimentation rate leads to an artificially high MA.[3] Thus sedimentation processes during the relatively long measurement periods may play a role. Also, clot formation in non-activated TEG is influenced by many factors. A study with non-activated TEG measurements alone might not be sufficient to explain these complex mechanisms.

Table 1 Mean (SD) TEG values before and after *in vitro* and *in vivo* dilution with 20% saline (n=12). *P<0.05 compared with control (Wilcoxon)

	Control	*In vitro* dilution	*In vivo* dilution
r (min)	7.9 (2.3)	5.8 (1.9)*	9.0 (2.9)
k (min)	4.8 (1.9)	2.6 (1.4)	5.0 (1.5)
MA (mm)	51.9 (6.1)	56.7 (6.5)	47.5 (5.7)

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1. Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *British Journal of Anaesthesia* 1996; **76**: 412–414.
2. Entholzner E, Calatzis AN, Kling M, Mielke L, Hipp R. *Anaesthesist* 1996; **45**: A171.
3. Lechner K. Blutgerinnungsstörungen In: Lechner K, ed. *Laboratoriumsdiagnose hämatologischer Erkrankungen 2.* Berlin, Heidelberg, New York: Springer, 1982; 177.

Sir,—We thank Dr Entholzner and colleagues for their comments. It is of interest that their *in vitro* studies confirmed our *in vitro* results,[1] despite the fact that they used citrated blood before performing the TEG studies. We have recently conducted some preliminary tests using immediately sampled blood and comparing it with the same blood citrated and then reconstituted with calcium in a manner identical to that recommended by the TEG manufacturers, that is 250 μl of citrated blood placed in the TEG cup to which is added 100 μl of 0.65% calcium chloride solution. Our observation was that the citrated and reconstituted blood clotted much more vigorously (shorter r and k times, steeper α angle and larger MA) than the non-treated controls. We are in the process of validating this observation at the present time. We are, therefore, sceptical that citrated blood truly represents the native state and that the results of Entholzner and colleagues may have reflected this.

The comment that the effect may be an *in vitro* phenomenon is of interest and we had already considered this possibility. A subsequent study of *in vivo* haemodilution has been performed by us and is currently under consideration for publication and we cannot, therefore, publish the data. However, in essence, this study showed a similar but slightly smaller phenomenon in the *in vivo* haemodilution compared with our *in vitro* experiments. We suspect that the difference observed by Entholzner and colleagues may be a result of their use of citrated blood.

As regards the difference between native and activated thrombelastography, we find their comments difficult to understand. First, the comment regarding the long r time of the control group in the study (9 min) makes no sense whether or not it refers to their letter or to our own data. It is true that the non-activated TEG measurement reflects only the activity of the intrinsic pathway. Whether or not the activated TEG truly reflects the activity created by the addition of tissue thromboplastins, such as occurs with tissue injury, is speculative and not supported to our knowledge by scientific evidence. While it is true that we speculated on several possible mechanisms for this phenomenon, in our subsequent *in vivo* study, we have also demonstrated a decrease in antithrombin III, thus confirming the possibility raised by Monkhouse that this may be at least part of the mechanism. Therefore, we cannot accept the suggestion of Entholzner and colleagues that our results are an *in vitro* effect. The article published by Ng and Lo[2] confirms that not only is this effect demonstrable *in vivo* but is demonstrable in the presence of major surgery where, presumably, activation of coagulation by tissue thromboplastins has taken place. We believe that our observations reflect a real clinical entity and not simply an *in vitro* aberration.

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1. Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *British Journal of Anaesthesia* 1996; **76**: 412–414.
2. Ng KFJ, Lo JWR. The development of hypercoagulability state, as measured by thrombelastography, associated with intra-operative surgical blood loss. *Anaesthesia and Intensive Care* 1996; **24**: 20–25.

Haemodynamic and neuroendocrine responses after pneumoperitoneum during cholecystectomy

Sir,—O'Leary and colleagues[1] investigated haemodynamic and neuroendocrine responses after pneumoperitoneum and body position changes during cholecystectomy.

Direct mechanical compressive effect on the abdominal aorta is unlikely to contribute to the increases in cardiac afterload and arterial pressure observed during laparoscopic surgery. Indeed, in human studies, haemodynamic alterations associated with laparoscopic surgery persisted for more than 20 min after pneumoperitoneum had been evacuated.[2] Moreover, an acute 9 mm Hg increase in abdominal pressure reproduced in a dog model the haemodynamic changes associated with laparoscopic surgery in humans.[3] Such a low pressure applied to the aortic high pressure system is unlikely to have induced the reported cardiac output redistribution towards the upper part of the body.[3]

Hypercapnia is unlikely to contribute to the haemodynamic changes associated with laparoscopic surgery. Indeed, during prolonged intraperitoneal carbon dioxide insufflation, carbon dioxide diffusion into the body has been demonstrated to be limited.[4] It results in a slight increase in Pa_{CO_2} accounted for by the increase in respiratory dead space caused by diaphragmatic impairment induced by increasing intraperitoneal pressure.[5] In the study of O'Leary and colleagues,[1] end-tidal $P\mathrm{CO}_2$ was easily maintained at 0.5–0.7 kPa.

Hormonal responses described during laparoscopic surgery have been shown previously to reflect the degree of surgical stress in "conventional" open surgery.[6] Vasopressin release paralleled the time course of the increase in systemic vascular resistances.[7] Changes in plasma concentrations of catecholamines, renin and cortisol were correlated with circulatory changes associated with general anaesthesia and reflect the stress response to surgery.[6–8] Changes in endothelin concentrations reflect tissue injury associated with surgery.[8]

More striking are studies showing that physical stimulation of intraperitoneal receptors increased systemic vascular resistances and arterial pressure.[9] Sympathetic nerve section significantly reduced circulatory changes not only in the presence of intraperitoneal physical stimulation but also in experimental intraperitoneal pressure elevation.[9]

We speculate that there may be involvement of baroreflexes elicited by various intra-abdominal viscera stimulation underlying the pathophysiology of circulatory changes associated with laparoscopic surgery in humans.

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1. O'Leary E, Hubbard K, Tormey W, Cunningham AJ. Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. *British Journal of Anaesthesia* 1996; 76: 640–644.
2. Westerband A, Van De Water JM, Amzallag M, Lebowitz PW, Nwasorka ON, Chardavoyne R, Abou-Taleb A, Wang X, Wise L. Cardiovascular changes during laparoscopic cholecystectomy. *Surgery, Gynecology and Obstetrics* 1992; 175: 535–538.
3. Robotham JL, Wise RA, Bromberger B. Effect of changes in abdominal pressure on left ventricular performance and regional blood flow. *Critical Care Medicine* 1985; 13: 803–809.
4. Mullet CE, Viale JP, Sagnard PE, Miellet CC, Ruynat LG, Counioux HC, Motin JP, Boulez JP, Dargent DM, Annat GJ. Pulmonary CO_2 elimination during surgical procedures using intra or extraperitoneal CO_2 insufflation. *Anesthesia and Analgesia* 1993; 76: 622–626.
5. Lister DR, Rudston-Brown B, Warriner B, McEwen J, Chan M, Walley KR. Carbon dioxide absorption is not linearly related to intraperitoneal carbon dioxide insufflation pressure in pigs. *Anesthesiology* 1994; 80: 129–136.
6. Chernow B, Alexander R, Smallridge RG, Thompson WR, Cook D, Beardsley D, Fink MP, Lake R, Fletcher R. Hormonal responses to graded surgical stress. *Archives of Internal Medicine* 1987; 147: 1273–1278.
7. McMahon AJ, O'Dwyer PJ, Cruik Shank AM, MC Millan DC, O'Reilly D St J, Lowe GDO, Rumley A, Logan PW, Baxter JN. Comparison of metabolic responses to laparoscopic and minilaparotomy cholecystectomy. *British Journal of Surgery* 1993; 80: 1255–1258.
8. Joris J, Lamy M. Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy. *British Journal of Anaesthesia* 1993; 70: A34.
9. Longhurst JC, Spilker HL, Ordway GA. Cardiovascular reflexes elicited by passive gastric distension in anesthetized cats. *American Journal of Physiology* 1981; 240: H539–H545.

Glycine absorption and hypocalcaemia

Sir,—I enjoyed reading the article by Dr Chassard and colleagues on the effect of glycine solution on calcium homeostasis[1] and would like to suggest an interpretation of their results. I have measured serum calcium concentrations during i.v. infusion of 1000 ml of glycine solution over 20 min in young men[2] and in prostatectomy patients.[3] A review of my original data shows that, during infusion, there was a close correlation between changes in serum sodium and albumin-corrected serum calcium concentrations. After infusion, however, serum calcium concentration was restored more rapidly than serum sodium concentration. Dr Chassard and colleagues also found a close correlation between serum sodium and free (ionized) calcium concentrations during the first 20 min of there study. Thereafter, serum calcium remained essentially unchanged, although the glycine infusion continued for another 40 min. All of these findings suggest that the mechanisms compensating for a diluted serum calcium concentration have the same strength as for serum sodium during 20–30 min of a glycine infusion, after which they become stronger for calcium.

Dilution of serum sodium during glycine infusions is governed mainly by the volume of irrigant absorbed. Correction occurs by diffusion of glycine and irrigant water from the extracellular to the intracellular fluid compartment, and marked, but delayed, cellular oedema develops.[4] Urine excretion also plays a part, but the urine contains large amounts of sodium,[2 3] particularly when a large volume of glycine solution is given.[5] The principal difference between the correction of diluted concentrations of sodium and calcium is that the latter ion can be mobilized easily from loosely bound bone stores, and equilibration has been claimed to occur with a half-time of 70 min.[6] The relatively poor perfusion of bone certainly explains some of this delay.

I believe that the time-course of this calcium mobilization can explain the absence of a further reduction of ionized calcium at 40 min and 60 min of the glycine infusions given by Chassard and colleagues. This indicates that hypocalcaemia probably does not get worse after 20–40 min of glycine absorption in the clinic either. When irrigating fluid is absorbed very rapidly, however, severe hypocalcaemia may develop within this time and then contribute to the hypokinetic circulation seen in the TURP syndrome.[7] A role for calcium in the treatment of this syndrome has also been suggested by two reports of patients in whom cardiac arrest and hyponatraemia developed during prostatectomy.[8 9] Some degree of "self-treatment" of the hypocalcaemia can be expected as the TURP syndrome is associated with metabolic acidosis, although this is usually fully compensated until circulatory disturbances occur.[10]

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1. Chassard D, Berrada K, Tournadre JP, Boulétreau P. Calcium homeostasis during i.v. infusion of 1.5% glycine in anaesthetized pigs. *British Journal of Anaesthesia* 1996; 77: 271–273.
2. Hahn RG, Stalberg HP, Gustafsson SA. Intravenous infusion of irrigating fluids containing glycine or mannitol with and without ethanol. *Journal of Urology* 1989; 142: 1102–1105.
3. Hahn RG, Stalberg HP, Ekengren J, Rundgren M. Effects of 1.5% glycine solution with and without ethanol on the fluid balance in elderly men. *Acta Anaesthesiologica Scandinavica* 1991; 35: 725–730.
4. Hahn RG, Nennesmo I, Rajs J, Sundelin B, Wroblevski R, Zhang W. Morphological and X-ray microanalytical changes in mammalian tissue after overhydration with irrigating fluids. *European Urology* 1996; 29: 355–361.

5. Stalberg HP, Hahn RG, Hjelmqvist H, Ullman J, Rundgren M. Haemodynamics and fluid balance after intravenous infusion of 1.5% glycine in the sheep. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 281–287.
6. Krohn JS. Dilutional hypocalcemia in association with dilutional hyponatremia. *Anesthesiology* 1993; **79**: 1136–1138.
7. Singer M, Patel M, Webb AR, Bullen C. Management of the transurethral prostatic resection syndrome: Time for reappraisal? *Critical Care Medicine* 1990; **18**: 1479–1480.
8. Charlton AJ. Cardiac arrest during transurethral prostatectomy after absorption of 1.5% glycine. *Anaesthesia* 1980; **35**: 804–806.
9. Malone PR, Davies JH, Standfield NJ, Bush RA, Gosling JV, Shearer RJ. Metabolic consequences of forced diuresis following prostatectomy. *British Journal of Urology* 1986; **58**: 406–411.
10. Hahn RG. Acid–base status following glycine absorption in transurethral surgery. *European Journal of Anaesthesiology* 1992; **9**: 1–5.

Sir,—We are grateful to Dr Hahn for his help in the discussion of our recent findings on the effects of glycine infusion on calcium homeostasis.[1] A readily exchangeable reservoir is responsible for 500 mmol of calcium exchange per day from bone to extracellular fluid. As he suggested, this could have contributed to the absence of further effect of glycine on ionized calcium after 20 min of i.v. infusion. However, the pH-normalized ionized calcium remained unchanged throughout the study, despite acute absorption of glycine (equivalent to 2000 ml for humans). As we concluded, changes in plasma sodium concentration rather than changes in calcium homeostasis are probably more important in the development of the TURP syndrome. As previous studies and Dr Hahn suggested,[2] we encourage further clinical studies, including monitoring calcium concentrations during acute TURP. This could help in the decision to introduce calcium therapy in the resuscitation of cardiovascular disturbances in this syndrome.

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1. Chassard D, Berrada K, Tournadre JP, Boulétreau P. Calcium homeostasis during i.v infusion of 1.5% glycine in anaesthetized pigs. *British Journal of Anaesthesia* 1996; **77**: 271–273.
2. Charlton AJ. Cardiac arrest during transurethral prostatectomy after absorption of 1.5 % glycine. *Anaesthesia* 1980; **35**: 804–806.

Locating an arterial foreign body by ultrasonography

Sir,—Shah, Downing and Davis described severance of a segment of catheter after arterial cannulation leading to embolization within the radial artery.[1] They reported that surgical exploration of the distal portion of the artery was unsuccessful and the fragment was finally retrieved after proximal radial artery exploration. We write to suggest that real-time ultrasound imaging might have been helpful by allowing rapid location of the fragment before surgical removal.

Lightweight, portable machines are available specifically for anaesthetic use (Site Rite, Dymax Corporation, Pittsburgh, PA, USA). These machines provide good quality images of vascular anatomy, especially in the neck, and their use as an aid to internal jugular vein cannulation represents an advance in safety and efficacy in adult[2] and paediatric patients.[3] The device can also be used to demonstrate the course and calibre of peripheral arteries. A short-focus probe (9 MHz frequency) with a focal length of 0.7 cm from the probe cap can easily identify an intra-luminal foreign body, which is displayed on the screen as a densely echogenic image. This allows rapid and non-invasive ultrasonic assessment of the radial artery "at the bedside". Sterile, acoustically transparent probe sheaths are available to allow aseptic examination.

We suggest that ultrasonic assessment in a situation such as this would permit confident localization of a wayward fragment and, if available, represents a potential advance in management.

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1. Shah US, Downing R, Davis I. An iatrogenic arterial foreign body. *British Journal of Anaesthesia* 1996; **77**: 430–431.
2. Troianos CA, Jobes DR, Ellison N. Ultrasound-guided cannulation of the internal jugular vein. *Anesthesia and Analgesia* 1991; **72**: 823–826.
3. Alderson PJ, Burrows FA, Stemp LI, Holtby HM. Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central vein cannulation in paediatric patients. *British Journal of Anaesthesia* 1993; **70**: 145–148.

British Journal of Anaesthesia 1996; 77: 812–814

BOOK REVIEWS

Regional Anesthesia and Analgesia. D. L. BROWN (editor). Published by WB Saunders, Philadelphia. Pp. 749; indexed; illustrated. Price £99.00.

This is an impressive reference book, with 750 pages and 59 authors, the stated aim of which is "to fill the need for a clinically focused textbook of regional anesthesia and analgesia". There is no doubt that it achieves this aim, albeit with a distinct bias towards North American practice; a more international blend of authors would add balance and avoid some of the parochialism that exists.

By dividing the book into five sections, the huge amount of information is easy to navigate. Section one could be omitted as it contains only the personal views of the editor on regional anaesthesia (better expressed as a foreword) and some history which rather emphasizes the minutiae of the early years of the American Society of Regional Anesthesia. Section two, "Basic science" is possibly the best in the book; it covers anatomy, neuroanatomy and neurophysiology in a refreshingly readable way, combining established facts with new data in a clinically relevant presentation. In rapidly changing areas such as regional anaesthesia and the stress response (chapter 7), no textbook can be totally up to date but this is a good summary of recent work. The section ends with pharmacology; chapter 8 by de Jonge ("Local anesthetic pharmacology") is a masterly climax and should be read by both examinee and examiner.

Section three "Induction of regional anesthesia" starts with a whimper—an irrelevant chapter on equipment and some repetitive pharmacology. It gets into its stride with the core detail of the book, the systematic description of central and peripheral nerve blocks from head to toe. If some techniques are described rather concisely for a beginner, it is because Dr Brown has a companion volume *Atlas of Regional Anesthesia* (very practical and lavishly illustrated) which he would wish the reader to buy.

While leaving room for disagreement with particular details of individual techniques, the chapters are well written with practical expertise and highlighted clinical notes to improve a novice's chances. The advice on managing the conduct of a block and subsequent patient care during and after surgery is eminently sensible and underlines the stated aims of the book. Chapter 19, "Neuraxial blocks", epitomizes the overall quality of this section and the ethos of the book itself.

Section four covers the expected (physiological) and unexpected (complications) effects of regional anaesthesia without too much repetition of earlier chapters, and section five discusses the use of regional anaesthesia in surgery, obstetrics and acute and chronic pain management. Inevitably, there is repetition, with some blocks being described several times in different parts of the book but minor criticisms aside, this section will repay time spent reading it. Of necessity, the chapters on pain are not comprehensive reviews of this major topic but more an attempt to put the use of regional anaesthesia into the correct perspective. Chapters 39 ("Outcome after extradural anaesthesia") and chapter 40 ("Pharmacology of pain control") are particularly good reviews of these very topical subjects.

There are some excellent books on regional anaesthesia and pain management currently available and a large, expensive textbook must be special if it is to succeed. The editor and publishers have done everything possible to ensure that this book will succeed. It is beautifully produced, with clear and informative illustrations which enhance the text.

H. B. J. Fischer

Key Topics in Anaesthesia. T. M. CRAFT AND P. M. UPTON. Published by Bios Scientific Ltd, Oxford. Pp. 341; indexed. Price £21.95.

This is the second edition of a book which has become one of the standard revision aids for trainee anaesthetists before postgraduate examinations. One either likes or hates this method of study for examinations. A quick flick through the book will readily indicate to which group one belongs. It is 341 pages of concentrated fact. If it had been around when I took my examinations I would certainly have purchased it.

There are 111 broad headings which could be considered as chapter titles from a larger textbook. These have then been arranged in alphabetical format. This does not necessarily make looking up individual topics easier. The book also has an index. However, *Key Topics* is not meant to be used in this way. It aims to provide a framework of information on key areas commonly appearing as topics in postgraduate examinations. In this it succeeds and should form a useful revision aid. In addition, at the end of each "chapter" there are very helpful lists of related topics of interest and suggestions for further reading. The references given are topical and in the main up to date.

The authors accept that the text is not comprehensive and some subspecialties such as intensive care, pain management and regional blocks are not well covered. (Perhaps these are areas for future inclusion in the *Key Topics* series.) However, there were also one or two omissions elsewhere. For instance, NCEPOD was covered but another favourite examination question on the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom was not included. Also, treatment of pre-eclampsia and the diagnosis and treatment of TURP syndrome were not well covered. These points apart, the book is an excellent aid to both the examination candidate and examiner. I would expect well used copies to be present in all trainees' brief cases.

N. R. Webster

The Pocket Companion to the Textbook of Critical Care Medicine. W. C. SHOEMAKER, A. GRENVIK, S. N. AYRES AND P. R. HOLBROOK. Published by WB Saunders, Philadelphia. Pp. 844; indexed; illustrated. Price £29.50.

Management of the critically ill is a difficult and often intimidating task for doctors in training. Combined with the recent increase in intensive care training requirements and the emphasis on a multidisciplinary approach to patient management, the publication of *The Pocket Companion to the Textbook of Critical Care Medicine* is well timed.

This text is intended to be a pocket book for the trainee doctor on intensive care assignment and aims to provide a step-by-step approach to the management of most clinical problems. Each chapter covers essential relevant physiology, patient work-up, monitoring and management. The range of topics covered is comprehensive and up to date, with particularly good chapters on paediatric and obstetric emergencies.

Although the text is generally readable, clarity is sometimes obscured by a long-winded prose style. The cook book approach used in the chapter on resuscitation is confusing and likely to prove difficult to follow in the "heat of battle". The algorithms included are detailed but lack impact because of the small print size. The absence of any references is disappointing and a little surprising. The book is, perhaps, more successful as a summary of the original *Textbook of Critical Care Medicine* than it is a convenient practical handbook for clinical use.

Although based on North American practice, this does not detract from the value of the book for a physician working in intensive care anywhere in the world. It can be recommended more as a useful addition to the ICU library than an essential purchase.

C. Hickey

Current Topics in Intensive Care, 3rd Edn. R. P. DELLINGER, H. BURCHARDI, G. J. DOBB AND J. BION (editors). Published by WB Saunders, London. Pp. 282; indexed; illustrated. Price £30.00.

This is the third in a series of pocket-sized texts which are published annually. It consists of 13 chapters, each with an extensive list of up-to-date references, written by 21 international contributors, nine of whom work in the USA. It has been written for both clinicians practising intensive care and trainees preparing for postgraduate examinations. Six of the chapters discuss clinical topics. These are balanced by four chapters of basic scientific information, pertinent to clinical practice, on: nitric oxide in circulatory shock; animal models for research; adhesion molecules; and formation and resolution of pulmonary oedema. There are also three reviews on modern radiographic imaging techniques, featuring Doppler echocardiography and transcranial Doppler ultrasonography.

The chapters covering clinical topics have been well written and provide a valuable review of their subjects. Therapeutic monitoring of commonly used drugs such as antibiotics, anticonvulsants, digoxin and cyclosporin is considered in depth; the economics of monitoring drug concentrations is also examined. The fundamentals of mechanical ventilation, which are essential knowledge for any intensivist, are considered over three chapters and the clinical problems associated with managing the acute asthmatic patient are also discussed. The hazards of a ventilator strategy based on preset volume goals are detailed: such practice may now seem outdated to many British anaesthetists. Dr Nicholas Hill has reviewed the role of non-invasive positive pressure ventilation, concluding that carefully selected patients with chronic obstructive airways disease are most likely to benefit from this new development. Clearly, non-invasive ventilation is an attractive alternative to tracheal intubation, but we have not yet found a role for it in acutely deteriorating postoperative patients. Mervyn Singer's review of early enteral feeding in the acutely ill patient reminds us of how much better this nutritional route is, not only for our patients, but also for our budgets. This will be preaching to the converted for most intensivists, but I fear that not all of our surgical colleagues are fully convinced!

Professor Eric Milne's chapter on imaging techniques in the critically ill patient considers the value of such modern technologies as computer tomography (CT), magnetic resonance imaging, ultrasound, angiography and nuclear imaging. His discourse on the plain chest x-ray will prompt me to look afresh at such films. However, considering the number of CT scans of head, thorax and abdomen performed on critically ill patients, I would prefer to have had the value of these investigations demonstrated by more illustrations. The chapter on echocardiography presents the background to Doppler imaging and shows how mathematical manipulation allows cardiac output, intracardiac pressures and pressure gradients across the heart valves to be measured non-invasively. Several clinical studies are reviewed, and the potential which echocardiography has to complement the invasive cardiovascular monitoring, now so commonplace in intensive care practice, is acknowledged.

The essay on adhesion molecules and tissue injury provides an insight into an important but complex area and suggests therapeutic approaches which may be developed. Professor Thiemermann explores the potential role for inhibitors of nitric oxide synthase in circulatory shock; these drugs are at present undergoing clinical trials in such patients.

In summary, I enjoyed reading this book, with its useful reviews of many scientific and clinical topics relevant to present day intensive care practice. At £30, the price is typical of books of this size, but is good value.

G. T. Taylor

The Anaesthesia Viva: vol.1. J. URQUHART AND M. BLUNT. Published by Greenwich Medical Media, London. Pp 161; indexed; illustrated. Price £12.50.

This book is yet another of those which aim to guide fellowship examination candidates to success. It comprises over 200 questions on the basic sciences section of the new primary FRCA examination. However, it makes no attempt to cover the entire syllabus, but we are promised volume 2 later this year.

The book is composed of 14 sections and three somewhat superfluous appendices. The subjects of the sections, 50% physiology and 50% pharmacology and statistics, reflect more or less the content of viva 1 of the examination. Cardiorespiratory topics make up the bulk of the first half and the remainder is reasonably well balanced. Pharmacology comprises 30% pharmacokinetics, pharmacodynamics and anaesthetic drugs, with the remainder divided fairly evenly, although statistics occupies only three pages. The format is that of question and explanatory answer, but the quality of the explanation is variable, for example "Can you draw the oxyhaemoglobin dissociation curve" is followed by the statement "If you cannot you will fail". This is unfortunate as the diagram then contains an error on the label of the x axis! Oversimplification in the explanation sometimes leads to confusion, for example a line missed in the derivation of the shunt equation fails to supply a logical sequence—not useful in a teaching book.

The sequence of questions is somewhat random in places; isolated facts without relating a concept to an overall systematic review leads to inconsistency, for example different values given for ECF volume in different discussions of fluid distribution. Many of the questions are examiners' favourites but may not appear in future "new exam" vivas! Similarly, there are old chestnuts (e.g. antibiotic interference with neuromuscular block) which are no longer relevant. There are sections on therapeutic regimens in a book purporting to be on basic physiology and pharmacology, but there is inconsistency in the absence of management guidelines in some subjects with a more fundamental physiological rationale.

The typeface is very clear and the pages are presented in a clean format, but there are several typographical errors in equations and diagrams, surely unforgivable in these subjects.

On the credit side, the book contains an enormous amount of factual material concentrated in an affordable volume. Some may enjoy this as a form of learning, where disjointed questions are supplied with explanations. A more organized approach could be gained by reading standard texts. As a means of self-assessment this format may have more to commend it. The preface, written by a member of the council of the College, gives important advice on using this book only as a supplement to standard texts, and this advice is reiterated at the end of the authors' introduction. It is perhaps premature to assess the value of a book on postgraduate examinations in anaesthesia at a time when the system itself is undergoing change. However, the book is a timely and commendable attempt to provide worthwhile assistance for the new generation of trainees in anaesthesia.

D. Fell

Perioperative Management for House Surgeons. P. R. HAMBLY AND M. C. SAINSBURY. Published by Bios Scientific Ltd, Oxford. Pp. 280; indexed; illustrated. Price £17.95.

This is an excellent book. The authors, two senior registrars in anaesthesia, state in the preface that they hope the book will provide help with those questions to which, at 03:00, no one seems to have the answers; the book certainly achieves this objective. The text is divided into two sections, the first dealing with preoperative issues and the second with postoperative problems. The final part of the book consists of short, sharp, succinct "action plans". The book covers all of the important areas involved in the perioperative management of patients. The style of writing is clear, to the point and often witty. The chapter on communicating with patients and colleagues is particularly well written and contains very useful advice for a new house surgeon. Indeed, the book is full of good, sound, practical tips and when I gave it to my own house surgeon to peruse I only got it back after a lot of pestering! The book can easily be read from start to finish as an educational exercise but, importantly, it is very well indexed and therefore easy to find information quickly. The action pages are particularly good. One minor quibble is that it would be nice to see an action page on postoperative chest pain.

In summary, the authors have achieved their intended aim admirably and the book provides a wealth of important practical management tips and pathways for the perioperative patient. I have written to my Trust Risk Management Committee to suggest that every surgical houseman is given a copy of this book—it will be money well invested!

N. J. M. London

Diagnostic Testing in Emergency Medicine. A. B. WOLFSON AND P. M. PARIS (editors). Published by WB Saunders, Philadelphia. Pp. 626; indexed. Price £30.00.

This is an easy to read reference guide to tests available to clinicians in the emergency situation, not only in accident and emergency, but also in hospital.

Broadly, it is divided into three sections: a general section with emphasis on tests used for paediatrics, pregnancy and the elderly; a second section on clinical syndromes, that is which test to do in a particular clinical situation (e.g. DVT); and a final section on diagnostic tests, taking each group of tests and discussing the value in specific situations based on the current clinical literature (e.g. CT scanning, neurological, with a sub-section on intracerebral haemorrhage).

The book has been published by American physicians and obviously, therefore, has a clear American bias with considerably more emphasis on tests in diagnosis, compared with the British more clinically based diagnostic process. However, our own clinical practice is gradually changing. Therefore, this represents a well discussed and thoroughly referenced manual, which makes it easy to understand with supporting further reading.

As we move into a more evidence-based system of medicine, any extra tests which we wish to perform have to be heavily justified to management. This, therefore, is a useful tool.

Provided one interprets this book with a British clinical point of view, it is a useful reference book for those involved in emergency care, destined, more reasonably perhaps, to the hospital or departmental library rather than one's back pocket.

D. N. Quinton

Handbook of Clinical Anaesthesia. J. C. GOLDSTONE AND B. J. POLLARD (editors). Published By Churchill Livingstone, Edinburgh. Pp. 722; indexed; Illustrated. Price: £50.00

This paperback is in a somewhat new format. The editors have persuaded a large number of contributors to produce sets of guidance notes for anaesthetic problems. The approach is problem-orientated within three sections: patient problems, surgical procedures and anaesthetic factors. Thus the order is as we might approach a patient—what are the general problems, what are the surgeons likely to do and what sort of anaesthetic problems may be encountered. This can lead to some duplication. For example, hyperthyroidism is discussed as a medical problem with advice as to perioperative management and later, by a different author, under the management of thyroidectomy. The thyroid operation also gets a mention under the difficult airway in the anaesthetic problem section. Such duplication is inevitable in this format but may well be a helpful reminder for anyone checking on a topic using the contents list rather than the index. But the list of topics is impressive: it covers virtually all the commoner medical problems and the types of surgery.

Each small review uses lists and a standard format. There are cross references to other chapters and usually a bibliography of recent articles. The general effect is of a helpful set of notes for those of us who meet the occasional unusual problem and a very helpful set for those taking examinations. There are the occasional infelicitous comments. For patients to undergo abdominal aortic surgery we are advised to "reassure the patient and maintain a calm environment" in the anaesthetic room. Don't all patients deserve this? Should we keep up the calm environment in the operating room and also afterwards? But this is a minor quibble; the book will be of practical help to most.

J. Norman

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Regional Anesthesisa and Analgesia, Brown, D. L., (editor), (*R*) 812

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——, Myocardial extraction of bupivacaine in anaesthetized sheep and by hearts of sheep and rats *in vitro*, Foth, H., *et al.* 257–264

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——, Pre-emptive analgesia with NSAID—what does it achieve? Morrison, L. M. M., *et al.*, (*C*) 129
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——, Glycine absorption and hypocalcaemia, Hahn, R. G., (*C*) 810–811
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The Anaesthesia Viva: vol. 1, Urquhart, J., *et al.*, (*R*) 813
The Cambridge Dictionary of Statistics in the Medical Sciences, Everitt, B. S., (*R*) 133–134
The Massachusetts General Hospital Hand Book of Pain Management, Borsook, D., *et al.*, (editors), (*R*) 134
The Pocket Companion to the Textbook of Critical Care Medicine, Shoemaker, W. C., *et al.*, (*R*) 812
Total Burn Care, Herndon, D. N., (editor), (*R*) 135
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